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CLINICAL EXPERIENCE WITH A NEW ANTITHYROID DRUG: 2-CARBETHOXYTHIO-1-METHYLGLYOXALINE*†

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SINCE the usefulness of the antithyroid drugs has been firmly established, investigators are constantly seeking new allied drugs which they hope will have improved qualities. Up to the present time, since Astwood's epochal introduction of thiouracil, the thyroid service of the Lahey Clinic has evaluated and reported on the clinical properties of many different substances (thiouracil, thiobarbital, propylthiouracil, methylthiouracil, methimazole and iodothiouracil). To this group we wish to add our experience with another member of the antithyroid family, neomercazole,® which chemically is called C.G.1, an abbreviation for 2-carbethoxythio-1-methylglyoxaline.

Neomercazole® (Fig. 1) resulted from the introduction of a carbethoxy group in place of the H-atom in the structural formula of tapazole® (1). Professor Rimington and his associates (of England) believed the addition of the carbethoxy group would slow the hydrolysis of the chemical and

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* Neomercazole®, supplied through the courtesy of Prof. C. Rimington and his associates of the University College Hospital Medical School, London, England, and the British Schering Corp., Ltd.

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This article will be included in the bound volume of the 1953 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for purchase early in 1954.

thereby prolong its antithyroid activity. The added radical was also found to render the substance tasteless as compared to other thiouracil preparations, which are extremely bitter. The acute toxicity of this new substance as tested in mice was found to be similar to that of thiouracil.

The initial report (2) on neomercazole® covered its use in 14 patients with Graves' disease. The total daily dose was 10 mg. In all cases there was rapid improvement in the patient's general condition. In most cases the basal metabolic rate fell markedly after three to five weeks. The fall

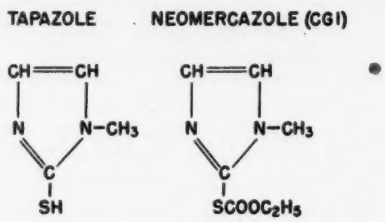

FIG. 1. A comparison of the structural formula of tapazole® (methimazole) with that of neomercazole.® In the latter, the H-atom in the tapazole structure is replaced by a carbethoxy group.

in pulse rate was not as noticeable as the general improvement, and the weight increased in only a few cases. No change was noted in the thyroid gland. It was reported that occasionally there was a decrease in the polymorphonuclear leukocytes, but this was counteracted by administration of vitamin B_6. Those patients submitted to thyroidectomy after treatment, although not given iodine, were said to have thyroid glands free of objectionable vascularity at the time of operation.

A more recent personal report (3) from Professor Rimington regarding the clinical use of neomercazole® indicated that approximately 200 patients have received this new substance and no side reaction of any sort was seen. Many of these patients probably are included in the reports just available from Doniach (4) and from Poate (5.) Doniach reported on 120 patients treated up to twenty-one months; neomercazole® was used in 30 cases in preparation for operation and in 90 as curative treatment. The suggested dosage ranged from 15 to 45 mg. daily, depending on the degree of hyperthyroidism. No toxic reaction was noted. Doniach was of the opinion that this new agent was as effective as methimazole (tapazole®).

Poate's report includes 9 patients treated with neomercazole.® He concluded from his experience that this new drug is superior to any of the thiouracil compounds now available. The dose suggested was 30 mg. daily. He also concluded that thyroid hyperplasia does not follow its use; thus, excessive bleeding at the time of thyroidectomy is avoided. Since no untoward reaction was observed, Poate thought it a safe remedy.

This study of neomercazole® was undertaken primarily in the search for an ideal antithyroid agent, one free from all side effects. It was also desired to establish the dosage required to bring about a consistent response similar to that obtained from a given dosage of the other antithyroid drugs with which abundant experience has already been gained.

CLINICAL MATERIAL

The new agent was given to 40 patients who had primary hyperthyroidism (Graves' disease) and to 12 patients who had adenomatous goiter with hyperthyroidism—a total of 52 patients. All ages were represented, from childhood to the seventh decade of life. Forty-nine patients were females and 3 were males. Those with primary hyperthyroidism had had the disease for an average of nine months and those with adenomatous goiter, for an average of thirty-five months. The weight loss resulting from the disease was variable. The maximum loss was 60 pounds; 18 patients lost more than 15 pounds. The basal metabolic rate ranged as high as +74 per cent; 22 patients had rates of +40 per cent or over. The findings indicate that all these patients had well established hyperthyroidism. In all patients, treatment was given in order to bring about a euthyroid state in preparation for a subtotal thyroidectomy.

DOSAGE

It was quickly determined that the suggested dose of 10 mg. of neomercazole® daily was insufficient to bring about a satisfactory clinical response. The dose was then gradually increased and it was finally determined that, for a patient with primary hyperthyroidism who had a small goiter, 30 mg. daily was required to produce a response equivalent to that obtained from a daily dose of 300 mg. of propylthiouracil or 30 mg. of tapazole.® When the goiter was large, 40 mg. daily was needed, as indicated in Figure 2. In this instance, a woman of 64 years who had severe primary hyperthyroidism of one year's duration, with a basal metabolic rate of +73 per cent, required sixty days of treatment with 40 mg. daily to restore her to a euthyroid state. This represents an approximate drop in the basal metabolic rate of 1 per cent per day—a very favorable response. Subtotal thyroidectomy was then performed, involving the removal of 43 Gm. of tissue, which is a fairly sizable goiter for a patient of this age.

Patients who had adenomatous goiters required larger doses, 40 to 50 mg. daily, in order to obtain the desired antithyroid effect. In Figure 3 is indicated the clinical response of a woman, 31 years of age, who had an adenomatous goiter with hyperthyroidism and a basal metabolic rate of +30 per cent. Two months of treatment with large doses of neomercazole® was required to depress the basal metabolic rate to −2 per cent, in order

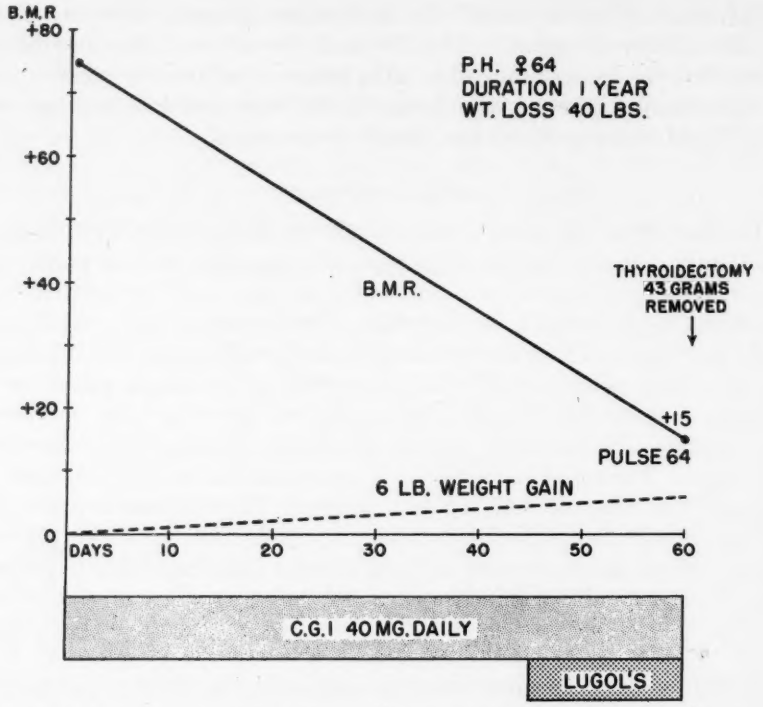

FIG. 2. The clinical response to neomercazole® of a patient with severe primary hyperthyroidism. After sixty days of treatment the basal metabolic rate was near the normal level, a drop of 1 per cent per day.

to permit a safe thyroidectomy. The basal metabolic rate fell at a rate of 0.5 per cent per day, which is a favorable rate of fall.

The experience with these 2 cases of hyperthyroidism was typical of that in other cases in this group of 52, and led to the opinion that the daily requirement of neomercazole® was 30 to 40 mg. for patients with primary hyperthyroidism—the larger dose for those with a sizable goiter or for those who had previously received iodine. A daily dose of 40 to 50 mg. is advisable for patients having adenomatous goiter—the larger dose for those with a sizable goiter. All of our patients started on this dose schedule responded satisfactorily. The fact that this is also the dose schedule used for patients given tapazole® suggests that these two drugs are similar in their antithyroid effect.

REACTIONS

It appeared extremely unlikely that the administration of neomercazole® would be free from side effects, since the structural formula is so similar

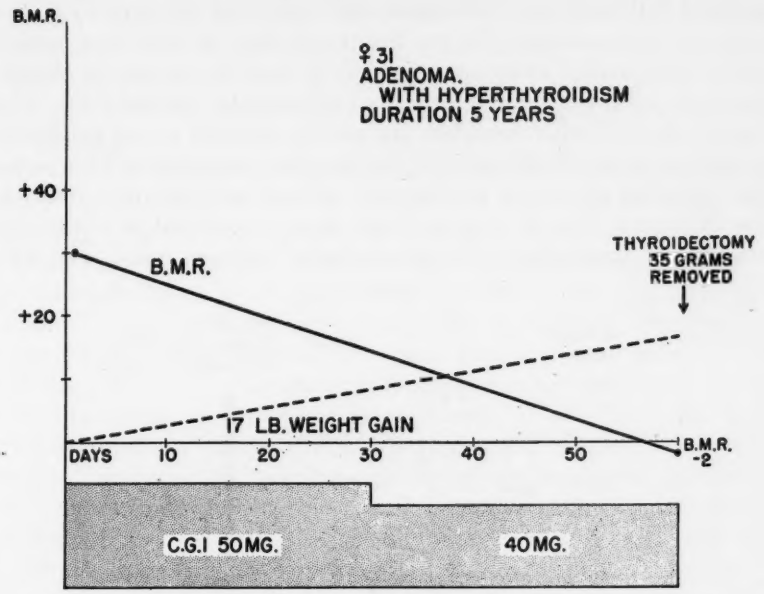

FIG. 3. The clinical response of a patient who had an adenomatous goiter with hyperthyroidism. After sixty days of treatment the basal metabolic rate was normal, a drop of 0.5 per cent per day.

to that of tapazole,® which has a reaction incidence of 6 per cent (6). Three reactions were observed in these 52 hyperthyroid patients while they were receiving neomercazole,® an approximate reaction incidence of 6 per cent (Table 1). In the first case listed in the table a nonpruritic, fine erythematous rash developed on the forearms and back six weeks after treatment was started with a daily dose of 40 mg. of neomercazole.® The daily dose was reduced to 20 mg.; thereupon there was some improvement in the rash, but it remained during the next three weeks while the drug was being administered. In the second case an extremely severe

TABLE 1. REACTIONS TO NEOMERCAZOLE® IN PRIMARY HYPERTHYROIDISM

Patient No.	Age and sex	Daily dose (mg.)	Day of onset of reaction	Type of reaction
1	59 F	40	42	Moderate nonpruritic, erythematous rash
2	32 F	50	14	Severe urticarial rash, angioneurotic edema and arthralgia
3	32 F	40	24	Agranulocytosis

generalized urticarial rash developed, with edema of the ears, eyes, neck and tongue. This occurred on the fourteenth day of treatment with 40 mg. of neomercazole.® Administration of the drug was promptly stopped. Response to an antihistaminic drug was slow and on the sixth day, when the rash had practically subsided, the patient suffered severe generalized arthralgic pains which necessitated bed rest for three days. This patient is now receiving potassium perchlorate[1] without any apparent difficulty. In the third case (Fig. 4) fever and sore throat developed on the twenty-fourth day of treatment with neomercazole,® 40 mg. daily. The white

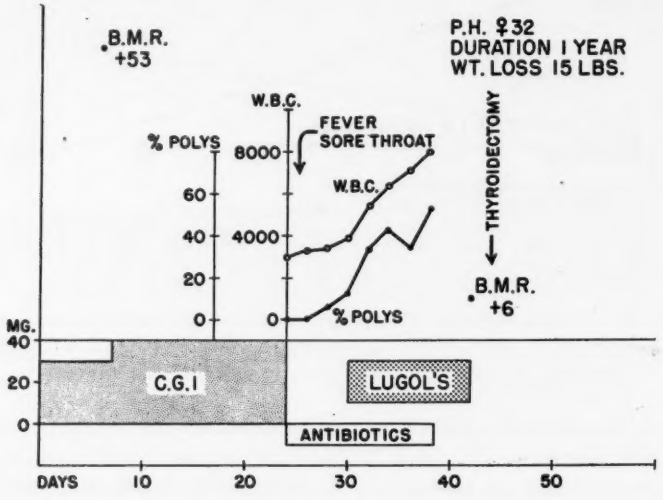

FIG. 4. On the twenty-fourth day of treatment with neomercazole,® agranulocytosis developed in this patient with primary hyperthyroidism. After fourteen days of treatment with antibiotics the blood returned to normal.

blood cells numbered 3,000, and polymorphonuclear cells were absent. A diagnosis of drug intoxication was made. The offending drug was withdrawn and energetic antibiotic therapy (penicillin and streptomycin) was instituted; in twelve to fourteen days the blood returned to normal. Since considerable antithyroid response was obtained prior to the drug reaction, only a brief period of therapy with Lugol's solution was needed to complete the preparation of this patient for operation; the basal metabolic rate prior to thyroidectomy was +6 per cent.

[1] A new antithyroid drug suggested by Dr. John B. Stanbury of the Massachusetts General Hospital Boston, Massachusetts.

SUMMARY

Clinical experience with a new drug, neomercazole® (C.G.I.), which has a structural formula similar to that of tapazole® (methimazole) with the H-atom replaced by a carbethoxy group, indicates that it is a potent antithyroid agent.

The dose of neomercazole® required for effective antithyroid action is similar to the effective dose of tapazole,® namely, 30 to 50 mg. daily, depending upon the type and size of the goiter under treatment.

When present, the side effects during the administration of this new agent were found to be similar to those seen during the administration of tapazole.® Three reactions occurred in the 52 patients who were given treatment, an incidence of 5.7 per cent. Of the 2 skin reactions which occurred, one was very severe but the other was not sufficiently severe to necessitate complete withdrawal of treatment. In the third case agranulocytosis developed on the twenty-fourth day of treatment; recovery followed the withdrawal of the drug and the administration of antibiotics.

The experience with this new drug indicates that, despite its strong antithyroid qualities, it is still not the ideal drug. Although side effects are few, there is the danger of agranulocytosis resulting from its use.

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TREATMENT OF SIMPLE GOITER WITH THYROID*

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MEDICATION with thyroid was first used in the treatment of simple nontoxic goiter at a time when little was known of the physiology of the thyroid gland. Though the results were most gratifying, this form of treatment was largely abandoned almost fifty years ago. An investigation into this curious state of affairs disclosed a sequence of events which is interesting but not unique, since it has occurred in the case of other effective therapeutic agents. The present report comprises a summary of the medical literature dealing with this subject and an account of results personally obtained over a five-year period.

HISTORICAL

Prior to the introduction of thyroid as a therapy for simple goiter, iodine in one form or another was used for many years. Even before the element had been discovered, preparations now known to contain iodine were in use. Local applications of burnt sponge were employed in Europe before the twelfth century (41), and the use of various substances of marine origin was known to early nineteenth century European and American physicians. After iodine had been discovered by French scientists attempting to extract saltpeter from seaweed during the Napoleonic Wars, Coindet, in 1820 (15, 16), promptly deduced that these purple crystals might be the active principle in both seaweed and sponge. The results of his therapeutic trials with preparations of this element were highly successful. Confirmatory reports soon came from both sides of the Atlantic (2, 14, 24) and, as a result, the treatment of goiter with iodine became established.

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During the latter half of the nineteenth century, the use of iodine became less popular because of the reported occurrence of "Jod-Basedow"—iodine-induced hyperthyroidism; nevertheless iodine has remained the most widely used medical therapy for simple goiter throughout the world. This has been furthered by the renewed interest which followed the work of Kimball and Marine in 1918 (27).

Just why iodine should be effective in the prevention and treatment of goiter was not clear for many decades, and even today there are some who question the generally accepted interpretation of its action. Although Chatin (11–13) published a series of papers in the 1850's establishing an inverse ratio between the incidence of goiter and the iodine content of the soil, air and water, serious doubt was entertained by many investigators as to the accuracy of his methods. Indeed, until Baumann (4) clearly demonstrated the presence of iodine in the thyroid gland in 1895, it was often questioned whether this element was in any way related to goiter or to the thyroid. Only in the last quarter-century, through the work of McClendon, vonFellenburg, Hercus, and others, has it been generally recognized that there is an iodine deficiency in most of the large endemic goiter areas of the world. The decrease in the incidence of goiter in these regions following the introduction of iodized salt has provided confirmation of the etiologic importance of iodine deficiency.

In spite of the results which have followed the demonstration of the importance of iodine in thyroid physiology, it remains apparent that not all instances of thyroid enlargement can be traced to iodine deficiency. Most sporadic goiters do not seem to have such an etiologic basis and most do not respond to treatment with iodine. Even before Chatin published his observations it was recognized that iodine was effective in only a certain proportion of goitrous individuals, even among those from endemic areas.

Between 1880 and 1890 it began to appear that the function of the thyroid gland was to secrete a specific substance necessary for the maintenance of adequate metabolism by most bodily tissues. It had been shown that "cachexia thyreopriva" could be prevented and normal health maintained in dogs whose thyroids had been transplanted into the peritoneal cavity. Finally, in 1891, Murray successfully treated myxedematous patients with subcutaneous injections of thyroid extract (34).

It was soon discovered that thyroid substance is effective by mouth, and that a dried, powdered preparation of the gland is as effective as the glycerin extract. The discovery of the remarkable sequelae of thyroid administration created a sensation in the medical world. Thyroid was tried for many other conditions, whether they represented clear-cut disease entities or not, and many claims were made for the new remedy which later could not be substantiated. Thyroid was recommended for

syphilis, neurologic disease, various dermatologic disorders and insanity. Any symptom which might be connected, however remotely, with one of the stigmata of myxedema was investigated. Although the function of the thyroid gland was incompletely understood, many articles of lasting merit emerged from this period.

Dr. Moyan Sunderland of Edinburgh is said to have been the first to suggest the use of thyroid in simple goiter (1, 31), but no actual publication by him on this subject could be found. The first published results of thyroid administration in this disease were by Reinhold (40), in 1894. It had been observed that the peculiar mental retardation and sluggishness of myxedema and early cretinism disappeared after thyroid therapy. Therefore Reinhold, at the suggestion of his chief, Emmenhaus, began the administration of raw sheep's thyroid to 6 insane patients who coincidentally had well developed, nontoxic goiters. There was no effect on the mental state of the patients, but 5 of the 6 goiters disappeared almost completely. The only failure was in a "cystic goiter." Since the patients were suspicious of any unusual procedure, the thyroid was prepared in as fresh a state as possible, minced with liverwurst, and spread on buttered bread. The patients were given from 6.0 to 7.5 Gm. of thyroid gland every ten to fourteen days. One female attendant, whose goiter had begun to increase in size and who had observed the remarkable effects on the patients, asked to be allowed to take some of the thyroid. She received only two doses, but her goiter also underwent a marked regression.

At approximately the same time, and independently, P. Bruns, Professor of Surgery at Tübingen, began a careful investigation of goitrous patients who were otherwise in good health. His first communication appeared in 1894 (7) and was a preliminary report on 12 patients. In 9 of these, the goiters either completely disappeared or underwent considerable regression in a period of from two to five weeks.

The following year (8) he prepared a more complete report on 60 cases and in 1896 summarized the results of treatment in a series of 326 goitrous patients treated with thryoid (9). This investigation was restricted to "parenchymatous goiter." His previous studies had shown that cystic goiter and malignant tumors of the thyroid did not respond and that Graves' disease became worse rather than better. The patients were from 3 to 57 years of age. At first they were fed raw sheep's or calf's thyroid; later they were given tablets of desiccated thyroid containing the equivalent of 0.3 Gm. of fresh thyroid gland—two tablets daily for adults and from one-half to one for children.

The results of his investigation are shown in Table 1. The goiter disappeared completely in 8 per cent of the cases, there was a marked diminution of thyroid size in 36 per cent, a considerable diminution in 30 per

cent and no response in only 25 per cent. The results were best in the younger patients and in those in whom goiter had developed most recently. Bruns declared, "One cannot deny that the treatment . . . worked only in hyperplastic goiter and there most successfully in relatively fresh cases, namely of childhood and adolescence—the greatest number of goiters begin about this age, however." There was a maximum reduction in the

TABLE 1. RESULTS OF THE TREATMENT OF GOITER WITH THYROID, REPORTED BY BRUNS IN 1896

Decade	No. of patients	Complete disappearance	Good response	Measurable response	Slight or no response
I	36	12—33%	21—58%	2—5%	1—3%
II	147	13—9%	64—43%	45—30%	25—18%
III	68	1—1.4%	20—30%	23—33%	24—35%
IV	34	—	10—30%	10—30%	14—40%
V	25	—	5—20%	8—32%	12—48%
VI	16	—	—	7—43%	9—56%
Total	326	26—8%	120—36%	95—30%	84—25%

size of the goiter by the end of two weeks in over 50 per cent of the cases.

A relapse occurred in about 75 per cent of the cases. This usually occurred about one month after treatment had been stopped, but occasionally not until three to four months had elapsed. Several patients took one tablet a day for the first two weeks of each month and thus prevented a relapse. Bruns stated, "The faster the goiter diminishes the faster it will recur. The longer a goitrous patient is given thyroid, the longer the period of time after treatment is stopped before the goiter resumes its growth."

It was felt that the main advantage of thyroid over iodine was that the former induced a much more rapid response and did not cause toxic symptoms. Bruns found that one could give a much smaller amount of iodine when administered in the form of thyroid than when used in the form of inorganic iodine. When he gave 100 to 200 micrograms of inorganic iodine daily to several goitrous patients there was no response, whereas the administration of thyroid containing the same quantity of iodine was followed by a prompt diminution in the size of the goiters.

Bruns also observed histologic changes in the thyroid glands of a group of goitrous dogs given thyroid. There was a progressive increase in the size of the follicles and a decrease in their number as the glands became smaller. The thyroid epithelium became flatter. There was a decrease in the blood supply of the glands from 20 per cent to 13 per cent by weight, and the connective tissue in the gland was increased. Similar changes were

subsequently found by Rienhoff (42) in human goiter treated with thyroid.

At the time Bruns made his observations, little was known of thyroid physiology, and it was widely believed that the function of the gland was to neutralize the "poisons" absorbed from the alimentary tract and that the signs and symptoms produced in athyreotic patients were due to the inability of such individuals to inactivate these toxins.

It is interesting, therefore, that Bruns' studies led him to conclusions which have a distinctly modern character. For example, the following, taken from Bruns (8), might have been written today; "Since the feeding is only effective in hypertrophic goiters, one can theorize that the goiter owes its existence to an increased deficiency of thyroid secretion in the organism which it can take care of by functional hypertrophy. The substitute ingestion of thyroid juice compensates for this hypertrophy and allows it to regress. In support of this is the fact that the goiters of children and adolescents disappear so rapidly with thyroid feeding. . . . A fact which confirms this concept a little is that, as I could observe in a large amount of material, after partial thyroidectomy the remaining portion of the gland has a tendency to become further enlarged. But these are only conjectures, since the etiology of goiter still lies largely in the dark."

"One would expect if the concept of 'Substitution Therapy' is correct that the danger of a relapse would be considerable. . . . Its significance is not too serious, however, since the recurrence can be caused to disappear in a similar manner by repeating a short course of thyroid administration."

As was the case with iodine, the pioneering investigations of Bruns and of Reinhold were followed by numerous confirmatory articles from France, Italy (17), India (43), England (34a), the United States (26), and elsewhere. The results obtained were similar to those of the initial reports. Stabel (45) studied 83 goitrous patients over a period of approximately two years. These were divided into two groups, one of which was fed raw calf or sheep thyroid and the other, thyroid tablets from the Dresden "Hofapotheke." The 25 patients fed raw thyroid were treated at least four weeks. The raw thyroid was given twice a week—8 to 15 Gm. per dose for adults and 4 to 10 Gm. for children. The ages varied from 12 to 25 years and apparently all patients were females. There was a complete disappearance of the goiter in 4 and a reduction in the remaining 21. Two of those with a complete remission had a recurrence when the thyroid therapy was stopped. Stabel believed, as did Bruns, that the longer the treatment was continued the slower the rate of relapse and that, conversely, the faster the goiter disappeared during therapy the more rapidly would it recur. He found that the thyroid tablets did not produce nearly as favorable a response as did the raw thyroid. Since the standardization of desiccated thyroid tablets was inadequate during that period, it is possible that

the poor results compared to those obtained with the fresh gland were due to improper preparations.

Angerer (1) treated 78 goitrous patients, beginning with 3 Gm. of raw thyroid per week, and gradually increasing the dose to 5, 8, and 10 Gm. per week. In all but "four to six" of the patients treated, a reduction in the size of the thyroid gland was observed; only the firm, fibrous goiters were not affected. Cysts were also uninfluenced, but the parenchymatous tissue lying around them underwent considerable regression. "Soft goiters—the simple hyperplasias and thyroid adenomas that are common at puberty respond the best to a few small doses. These goiters also respond well to iodine, but the action of thyroid is much more rapid and one doesn't run the danger of 'iodism' (skin eruption, etc.)." He also cited 2 patients in whom iodine had no perceptible effect but who were "cured" by the administration of thyroid.

Knoepfelmacher (29) reported similar results in a series of 22 patients treated with thyroid tablets prepared by Burroughs, Wellcome & Company. In 11 the goiters almost completely disappeared and in only 5 was no change apparent. In the group with the most favorable results he reported 2 cases of single adenoma, one in a 2-year-old child and the other in a 16 year-old girl; both adenomas disappeared rapidly with thyroid therapy. The nodule in the girl was "nut-sized" and had been enlarging fairly rapidly before thyroid therapy was instituted. His explanation for the infrequent recurrence of goiters after omission of treatment was, "the thyroid enlarges in the first place because the demands upon it are too great. When thyroid is given it allows the gland to atrophy and rest, thereby becoming more efficient and serviceable so that when treatment is stopped the gland does not need to hypertrophy."

Kocher (30) reported a favorable result in 9 of 12 patients under 18 years old. He concluded, "It is now permissible to say that the ingestion of thyroid substance works similarly to the use of iodine preparations in hyperplastic goiters, in so far as it causes a disappearance of the hyperplastic gland substance. Colloid nodules are less influenced the longer they are present, since regressive changes following hemorrhages, disturbances of circulation, degeneration of vessels and connective tissue proliferation have already begun in these."

The first American report appears to have been made by Ingals and Ohls (26) in 1895. They employed desiccated sheep's thyroid made by Armour & Company, 6 grains being equivalent to one average entire gland. Fifty cases were reported, of which 6 were treated by them personally. The swelling was reduced in 38 of these. Large doses were employed in the treatment of some of these patients—as much as 30 grains per day. This was apparently not unusual, since mention is made in the article

that even some patients with myxedema received this large a dose. With the ingestion of such excessive amounts of thyroid, it is not surprising that over two-thirds of the patients in this series complained of headaches, dizziness, trembling, rapid pulse, weakness, nausea and weight loss. The authors felt that the symptoms usually occurred when a daily dose was reached (9 to 12 grains of dried gland) which corresponded to 1½ or 2 entire sheep thyroid glands. They were apparently accustomed to the use of much larger doses than the Continental investigators, since they recommended that although the dose of thyroid should not exceed 2 grains three times a day at first, this dosage could later be increased to two to three times that amount.

One might have anticipated, in view of the many other clinical reports of the favorable effect of thyroid on simple goiter (3, 10, 23), that such therapy would rapidly have become established. Oddly enough, such did not prove to be the case. For reasons, as yet unclear, this treatment never became widely accepted, and even today most of the current American textbooks of medicine either do not mention it or only note casually that it may perhaps be tried for the treatment of patients in whom hypothyroidism coexists with thyroid enlargement.

As early as 1901, Colbertaldo (17) noted that thyroid therapy of goiter was passing out of favor. Several unfortunate incidents occurred at the turn of the century which may have contributed to the neglect of this treatment during the ensuing years. Owen, an English practitioner, reported a case of exophthalmic goiter in 1893 which underwent a remarkable remission, including disappearance of the goiter, subsidence of signs and symptoms, and almost complete disappearance of the exophthalmos following treatment with raw thyroid (36). Two years later he reported that, due to the butcher's poor anatomic training, the patient had been receiving *thymus* instead of thyroid (37). He then went on to report 2 other patients who were greatly improved by thymus therapy (37). This led to a number of studies concerning the therapeutic effectiveness of the thymus. Some investigators published articles confirming Owen's claims. Even Mikulicz stated that thymus-feeding was good treatment for thyrotoxicosis and that it was as effective as thyroid treatment in simple goiter (33). Most clinicians eventually concluded that thymus was of little value in the treatment of goiter (28), however, and the treatment appears to have been discarded. It is possible that the disappointing results with thymus may, by some unreasonable association, have led to the abandonment of thyroid therapy. Also, many of the remedies for thyroid disease which were widely accepted at that time have since been found to be valueless. For instance, Murray, the first man to show the effect of thyroid administration in myxedema, stated in 1905 that one of the most

effective therapies of thyrotoxicosis was passing an electric current from one side of the neck to the other (35). It is possible that the use of thyroid in simple goiter may have been grouped with many other useless treatments of the day.

In the years since, the use of thyroid in simple goiter has rarely been mentioned in the literature, and the work of Bruns, of Reinhold, and of the other investigators of that era seems to have been entirely overlooked. Beebe, in 1916, in an article entitled "Therapeutic Applications of Human Thyroid Extract," mentioned it as being useful in hypothyroidism, dysmenorrhea, and the toxemias of pregnancy, but said nothing of the treatment of goiter (5). Plummer, in 1921, describing the clinical effects of the recently discovered thyroxine of Kendall, noted that twelve to twenty-four hours after the administration of this substance to patients with diffuse colloid goiter, the thrill disappeared, the vessels and gland decreased in size, and in three to four weeks the gland was barely palpable (39). Yet he made no mention of the earlier work on this subject and, indeed, did not recommend that thyroid or thyroxine be used in the treatment of nontoxic goiter.

Means, in 1922, thought that only "in certain types of goiter there may be an indication for the administration of thyroid and thyroxin. . . . In certain diffuse colloid goiters . . . there may be an actual deficiency of thyroid secretion available for the tissues. The goiter under such circumstances is the result, not the cause, of the hypothyroidism. In cases of this type . . . the administration of thyroxin will diminish the size of the gland and fails to produce the symptoms which thyroxin would in a normal person. These patients have metabolic rates of 8 per cent to 15 per cent below the average normal (32)." Soley, writing in 1938 on the clinical management of goiter, recommended iodine and made no mention of thyroid treatment (44).

Dorsey published an article in 1925 entitled, "How Much Have We Advanced in Our Observation and Treatment of Goitre during the Past Century?" (18). Despite the inclusion of iodine and such therapy as injections of boiling water, mercury inunctions and dietary revisions, the use of thyroid was omitted and was also not recorded in the rather extensive discussion from the floor which followed. Even in the country in which the pioneer investigations were conducted, the results were lost. Hahn did not mention thyroid therapy in a 1932 monograph from Berlin on the treatment of goiter (22). Other examples of such oversight are easily found (19).

The knowledge of thyroid therapy had not disappeared completely, however. Bram (6), in 1924, although giving no reference to previous work, stated, "Prophylaxis and treatment of endemic goiter is largely based on the theory that there is a lack of iodine in the thyroid gland. Accord-

ingly . . . administration of the proper quantity of iodine . . . is successful in the prevention and treatment of goiter in the majority of cases. In general, this is true of endemic, but not of sporadic simple goiter. . . . To employ iodine in sporadic goiter may benefit a small percentage of patients, but in the greater majority no change in the goiter will result. . . . There is a 'something' in thyroid substance which is more or less specific in the prophylaxis and treatment of sporadic simple goiter. . . . It is very difficult . . . to decide in advance which patient will react promptly and which slowly to thyroid extract. One patient may require but $\frac{1}{8}$ grain daily to procure the desired results, another not less than 5 grains. . . . Thyroid extract is administered on the assumption that the organ is incapable in its normal size of supplying the body with the required quantity of hormone."

In a few centers of medical teaching, the glandular therapy of goiter was sometimes revived. Rienhoff described in 1940 a "number of patients," including 6 in detail, in whom desiccated thyroid caused a marked reduction or disappearance of goiter, associated with a low metabolic rate (42). He first began such treatment because 2 sisters, aged 16 and 18, had large goiters and symptoms of hypothyroidism. Iodine had no effect on the goiters but when thyroid was given because of the hypothyroidism, there was a complete disappearance of the goiters in six months.

In view of the current infrequent use of thyroid in simple goiter, the following studies are presented. The results demonstrate the effectiveness of this treatment, confirming the claims made sixty years ago.

OBSERVATIONS

Clinical materials and methods

During the five-year period from 1945 to 1950, a group of 50 referred patients found to have simple nontoxic goiter was treated with thyroid and observed for a sufficient length of time to be included in this study. The usual dose was 2 or 3 grains daily, with the extremes varying between $\frac{1}{2}$ and 6 grains per day. Often the initial dose was later increased and in some instances there were several increments in dose. In more than half of the patients determinations were made of the uptake of radioactive iodine by the thyroid gland, and in many of these, one or more further determinations were made after thyroid therapy had been started. Increases in dosage were made if the 24-hour radioiodine uptake was found not to be suppressed to below 10 per cent of the quantity given. The patients were re-examined at intervals which varied from one week to two months, and therapy was continued until no further decrease in the size of the thyroid seemed likely or until the goiter had disappeared altogether.

As an exactly comparable series of untreated patients could not be ac-

cumulated, a survey was made of the hospital records of all patients entering since 1933 and found to have simple nontoxic goiter. Letters were sent to these patients and the 40 who returned for re-examination were used for the analysis.

The types of thyroid enlargement were classified as diffuse goiter, multinodular goiter, and single nodule. The outcome was classified as a complete regression when the thyroid became no longer visible or palpable or when it was of normal size by palpation, as a partial regression when

TABLE 2. RESPONSE OF THE THREE TYPES OF THYROID ENLARGEMENT TO TREATMENT WITH THYROID, AND THE OUTCOME IN A SERIES OF UNTREATED CASES

Type of thyroid enlargement	Response to treatment			
	No. of Cases	Complete regression	Partial regression	No change
Diffuse goiter	23	10	10	3
Multinodular goiter	9	3	3	3
Single nodule	18	7	5	6
Total	*50*	*20*	*18*	*12*
	Course without thyroid therapy			
Diffuse goiter	26	4	0	22
Multinodular goiter	6	0	1	5
Single nodule	8	1	0	7
Total	*40*	*5*	*1*	*34*

decrease in size was undoubted but incomplete, and as no change when there was no clear-cut decrease in size.

Results

A summary of the effects observed has been made in Table 2. Of the 50 patients treated, 24 per cent failed to show any response; 76 per cent experienced a regression in thyroid size and in 40 per cent the regression was complete. In the small series of multinodular goiters and single nodules, the response was less favorable than in the diffuse ones. However, in these 27, only one-third failed to show some effect. In contrast, among the 40 patients who received no thyroid therapy, only 6 experienced a decrease in thyroid size.

In an analysis of various factors which might contribute to the response to therapy, consideration was given to the size of the goiter, the age and sex of the patient, the uptake of radioactive iodine, the duration of the

TABLE 3. AN ANALYSIS OF VARIOUS FACTORS POSSIBLY CONTRIBUTING TO THE RESPONSE TO THYROID THERAPY

Type	Response	No. of patients	Age*†	Sex		Size of goiter†			Duration (yrs.)*†	Family history		Uptake of I^{131}†			Dose of thyroid (grains)*	Duration of treatment (mos.)*	Follow-up (yrs.)*
				M	F	+	++	+++		+	0	L‡	N	H			
Goitrous patients not treated with thyroid																	
Diffuse	Complete	4	42(13–65)	1	3	3	1	0	14(1–26)	—	3	—	—	—			12(6–18)
	Partial	0															
	No change	22	36(11–70)	2	20	11	11	0	9(1–18)	5	7	—	4	1			5(1–10)
Multi-nodular	Complete	0															
	Partial	1	54	1	0	—	—	1	2	—	—	—	—	—			4
	No change	5	43(36–56)	1	4	0	5	0	8(1–18)	3	1	—	2	—			3(1–6)
Single nodule	Complete	1	25	—	1	1	—	—	1	—	—	—	—	—			1½
	Partial	0															
	No change	7	45(23–57)	0	7	2	5	0	8(1–14)	1	1	—	2	—			5(2–9)
Goitrous patients treated with thyroid																	
Diffuse	Complete	10	31(17–46)	0	10	5	4	1	5(<1–12)	3	3	—	1	5	3(1½–6)	3(1–6)	1½–(<1–4)
	Partial	10	36(22–55)	1	9	2	5	3	6(<1–14)	1	2	—	6	—	3(2–6)	3(1–6)	1½–(<1–5)
	No change	3	45(35–57)	0	3	0	2	1	5(1–12)	1	—	—	1	—	5(2–6)	4(1–7)	2(<1–4)
Multi-nodular	Complete	3	48(32–57)	1	2	0	3	0	6(<1–12)	1	—	1	1	—	2(½–3)	3(2–5)	1(<1–2)
	Partial	3	48(35–57)	1	2	0	2	1	8(4–13)	1	2	—	2	—	3(2–5)	3(2–5)	<1(all <1)
	No change	3	48(37–65)	1	2	0	1	2	6(<1–11)	1	2	1	2	—	3(½–4)	7(6–8)	1(<1–2)
Single nodule	Complete	7	38(20–54)	2	5	1	6	0	1(<1–3)	—	2	—	3	—	2(½–3)	2(½–5)	2(<1–7)
	Partial	5	37(17–56)	0	5	0	5	0	5(<1–13)	2	1	—	3	—	3(3–6)	2(½–4)	1(<1–2)
	No change	6	39(26–47)	0	6	0	6	0	2(<1–4)	1	3	—	1	—	3(1–4)	8(2–12)	2(<1–5)

* Mean and range.

† When first seen.

‡ L, N and H—Low, Normal and High—refer to 24-hour I^{131} uptakes of less than 15 per cent, from 15 to 50 per cent, and more than 50 per cent, respectively.

thyroid enlargement, the influence of previous treatment, and the dose and duration of the thyroid therapy (Table 3).

Size.—It was difficult to devise an adequate system for grading the degree of thyroid enlargement. An estimation of the actual weight of the gland would perhaps have been best, but clinical estimates of gland weight are notoriously inaccurate. In the case of the single nodules, an estimation of thyroid weight would not adequately describe the size of the nodule. It was decided that the best, though unsatisfactory, method would be to make the judgment entirely subjective. Slight (+) enlargement indicated that the gland was definitely larger than normal and easily detected by palpation, but not large enough to be noticed by the casual observer. Moderate (++) enlargement indicated that it could be easily seen as well as felt to be enlarged, but did not make the patient cosmetically unattractive. If the enlargement produced definite disfigurement because of its size, it was considered to be great (+++). Most of the patients in all groups were classified as having moderate enlargement, although 43 per cent of the diffuse goiters were classified as slight. The size of the goiter did not seem to influence greatly the response to therapy, except that those patients with great thyroid enlargement seemed less likely to experience complete regression. In none of the nodular goiters with great enlargement and in only 1 of the diffuse goiters so characterized did a complete remission occur.

Age.—The ages of the patients ranged from 11 to 70 years. Those with diffuse goiter tended to be younger and those with nodular goiter, older than average.

Age did not seem to be a factor in the response to treatment; the average age of the patients whose thyroid enlargement disappeared completely did not differ from that of the group as a whole.

Sex.—There were 11 males and 79 females in the series, a ratio of 1:7. This is a higher proportion of females than most studies show, the most frequent differential being about 1:4. The number of males was too small to tell whether there was a sex difference in the response to therapy, but at least a large difference was not evident.

Radioiodine studies.—Among the 18 patients with diffuse goiter who were studied with radioiodine, one-third showed a 24-hour accumulation in the thyroid gland of more than 50 per cent of the administered dose. Of the 6 patients studied who experienced complete remissions, 5 showed an elevated thyroidal accumulation of radioiodine. Since the high uptake in these patients is believed to be associated with a hyperplastic, hyperfunctioning goiter, one might expect that a high uptake would predicate a good response to thyroid therapy. The length of time the goiter had been present did not seem to influence the radioiodine uptake, since some of the

patients with high uptakes had had goiter for more than ten years, whereas others had noted the goiter for only a few months.

There were 2 instances of abnormally low uptakes (less than 20 per cent) and both were in patients with nodular goiter. One was a moderate-sized goiter in a 52-year-old man, which had been noted only a short time before. This disappeared completely after two to three months of thyroid therapy and had not recurred when he was last seen one year later. The other was in a 45-year-old woman with a moderate-sized goiter, also of recent origin, which was not affected by over six months' treatment with 3 to 6 grains of desiccated thyroid daily.

Duration of the enlargement.—In general, the single nodules had been present for the shortest period of time and the nodular goiters the longest, although there was a good deal of variation. It was impossible to state exactly how long thyroid enlargement had been present. Sometimes a moderate-sized goiter is quite unnoticed by the patient and occasionally an accumulation of fat in the anterior neck region is mistaken, even by the physician, for thyroid enlargement.

In any event, the response to thyroid therapy did not seem to depend upon the length of time the goiter had been present, to as great an extent as it did in the studies of the earlier investigators. Of both the diffuse and multinodular goiters that disappeared completely, one-third had been present for less than one year, and one-third for more than ten years. Only in the case of the single nodules which underwent complete remission did the duration seem to be of importance, since all but 1 had been present less than one year.

Previous treatment.—Nineteen of the patients had previously received either iodine or thyroid therapy. As far as the patients were aware, the previous treatment caused no change in the size of the gland, with 3 exceptions. One man noted a definite decrease in the size of the gland after taking 2 grains of thyroid for one month. A young girl from the control group without thyroid therapy had had a complete remission induced by iodine. A third patient, a 21-year-old girl with a 3-cm. single nodule, had had a nodule in the same place when she was 13 years old. This had completely disappeared with iodine and she had had no recurrence until the seventh month of pregnancy at the age of 20. The nodule again disappeared completely after two weeks' therapy with 3 grains of thyroid daily. The patients who had previously taken thyroid to no avail but who showed a good response during the present investigation apparently either received inadequate dosage or took the drug for too short a period of time.

Dose of thyroid.—The majority of patients received 2 to 4 grains of U.S.P. thyroid daily. No patient received a dose of more than 6 grains per day. Patients whose goiters disappeared completely received a lower

average dose than the others, since there was a tendency to increase the prescribed amount of thyroid if the response did not appear to be optimal.

Some of the patients showed signs of mild hyperthyroidism when taking more than 3 grains daily. This was indicated by loss of weight, an increase in the heart rate, and occasionally increased nervousness, sweating, and tremor of the hands. Such reactions were not encountered when a dose of 3 grains daily or less was given, and they were never severe enough to necessitate the interruption of therapy.

The amount of thyroid necessary to cause complete disappearance of the goiter was small in some individuals. Three patients had a complete remission while taking less than 1 grain daily. It is possible that a larger number of patients would have responded to small doses had they been employed more often.

Duration of treatment.—In almost all patients treatment was continued only until a complete remission had been reached or until it seemed unlikely that further benefit might be expected. There was no difference among the three types of goiters with regard to the length of time required for them to disappear completely with therapy. Most complete remissions occurred within three months and none required more than six months. A patient with a 3-cm. single nodule had the most rapid response. The nodule was no longer detectable to either inspection or palpation after two weeks' treatment with 3 grains of thyroid daily.

It is possible that some patients who experienced a partial but inadequate response to therapy may not have been treated for a sufficient length of time. Most patients in this group were treated for less than three months. Of those patients who failed to show any response, however, most were treated for longer than six months, and it is unlikely that a prolongation of therapy would often have been effectual.

Relapses.—In only 2 instances did the goiter return after treatment was discontinued. In some cases the patients were observed for less than one year after treatment had been stopped, so that adequate evaluation was not possible. If one assumes that goiter is a physiologic response to meet the requirements of the body for thyroid hormone, one would expect that the cessation of therapy would regularly be followed by a return of the goiter. That this is not the case indicates either that the factors impairing thyroid function or those increasing the requirements of the body for thyroid hormone may be operative only temporarily, or that the thyroid gland can in some manner become more efficient after having been put at rest. The latter possibility was first suggested by Knoepfelmacher (29) and Lanz (31) in 1895. Earlier investigators were also impressed with the infrequency of relapses, although Bruns (9) reported that 75 per cent of his series had a recurrence. It is possible that with a longer period of ob-

servation more of the patients in the present series will exhibit a recrudescence of thyroid enlargement.

Course of disease without thyroid therapy.—Of the 40 patients who were not treated with desiccated thyroid, only 6 showed a decrease in thyroid size. Four diffuse goiters and 1 single nodule disappeared completely, and 1 nodular goiter underwent a moderate reduction in size. One of the patients with a diffuse goiter was 13 years old when first seen. The moderate-sized goiter gradually disappeared with iodine therapy and when seen eighteen years later there was still no evidence of thyroid enlargement. Two other patients with diffuse goiter had known of thyroid enlargement for more than ten years, and one for seven years. All 3 were over 40 years old when first seen. One had had an inadequate, short trial of desiccated thyroid before she was first seen, and one a course of treatment with iodine, but in neither case had any effect on the goiter been noted. All 3 of these patients reported a gradual reduction in the size of the goiter without treatment and when they were re-examined from six to ten years later the thyroid gland was not palpable in any.

The patient whose single nodule disappeared without therapy was a 25-year-old girl who had noted a nontender swelling in the right side of the neck several weeks before admission to the hospital. This was found to be a firm, discrete thyroid nodule approximately 2.5 cm. in diameter which had already begun to decrease in size before her admission. The nodule continued to diminish in size without therapy of any kind and had completely disappeared several weeks later. When last seen nineteen months after the initial visit, there had been no recurrence.

DISCUSSION

The results of earlier investigators concerning the usefulness of thyroid in the treatment of simple goiter were amply confirmed by this study. The age of the patient and the duration of the goiter prior to treatment did not seem to have as great an influence on the response to therapy as had been previously found. Many of the patients who experienced a satisfactory response were in the older age group and had noted thyroid enlargement for five to ten years or longer. This is in contrast to the findings of the German clinicians, who reported that there was a much lower incidence of remission in older patients and in those with goiters which had been present for a long time.

It was confirmed, however, that diffuse goiter is more apt to respond than the nodular variety. This would be expected, since the nodular goiters are usually those which have been present for many years; they have become densely infiltrated by fibrous tissue in many areas, and some of the nodules may represent old, organized hemorrhages or calcifications. In

view of the earlier reports, it could not have been anticipated that nodular goiter would respond to therapy. However, two-thirds of the goiters treated responded, and one-third disappeared completely.

Suggested mechanism.—Presumably the thyroid gland enlarges when, in its normal size and functional state, it is no longer able to supply the body's requirements. A decrease in circulating thyroid hormone occurs which leads to increased secretion of thyrotropin by the pituitary, which, in turn, causes increased growth and function of the thyroid gland. When enough thyroid hormone is again being produced to satisfy the requirements of the organism, the increased blood concentration will once again inhibit the production of excess thyrotropin and the finely adjusted balance will continue. Under certain circumstances, such as prolonged thiouracil or thiocyanate administration, the thyroid may never be able to produce sufficient hormone and the gland will continue to enlarge until its natural limits of growth have been reached.

Feeding thyroid to nontoxic, goitrous patients should induce a maximal suppression in thyrotropin secretion when enough hormone to satisfy homeostatic requirements is thus being supplied. That such requirements are usually not above those of nongoitrous euthyroid subjects is indicated by the finding that the thyroidal radioiodine uptake is suppressed to myxedematous levels by doses of thyroid which had previously been found to be needed in the normal individual (20). The increased uptake of radioactive iodine in hyperthyroidism is much less affected by the administration of thyroid (21)—a fact that may be of diagnostic value in doubtful cases.

With the exception of iodine deficiency and "struma medicamentosa," caused by the prolonged ingestion of antithyroid substances such as thiouracil or thiocyanate, the etiology of simple goiter remains obscure. It is possible that in some instances the ingestion of foods such as turnips and related vegetables which contain the antithyroid compound l-5-vinyl-2-thiooxozolidone may be responsible for the development of thyroid enlargement, but in the present series this could not be proved an etiologic factor. It is further possible that the ingestion of very small amounts of antithyroid compounds in food may eventuate in goiter, if the intake of iodine be suboptimal. Finally, in some instances of nonendemic goiter, there may be an inherent biochemical defect in the thyroid gland which impairs its efficiency to such an extent that enlargement is required to ensure adequate function. The latter possibility is suggested by the goitrous families with hypothyroidism studied by Rienhoff (42) and by Stanbury and Hedge (46), and further indicated by the high familial incidence in the series of patients reported here.

Although iodine therapy has been recognized as effective in endemic

goiter, it has been generally realized that it is of little value in sporadic goiter. Iodine may be effective when iodine deficiency is the major etiologic factor, or when the primary defect is a failure of the iodide-concentration mechanism of the thyroid. If, however, the defect lies beyond the stage of iodide concentration, such therapy might well fail.

Thyroid, on the other hand, will decrease the secretion of thyrotropin and, in turn, the size of the goiter, regardless of the nature of the defect in hormone synthesis; it therefore might be regarded as a specific in the treatment of goiter. As Angerer remarked in 1896, "There is no doubt that the specific organic iodine-binding that is present in the thyroid gland has a much more favorable action on the (goitrous) human organism than the iodine preparations which have been used up to now. Thyroid has a much more rapid action than iodine because iodine only helps in building the specific thyroid substance while thyroid therapy provides the finished product." (1). Moreover, if an interference in iodine binding is the mechanism responsible for the development of goiter, additional iodine could not be expected to be beneficial.

As a practical therapeutic measure the administration of thyroid has certain advantages. In addition to its beneficial effect upon the size of the goiter in 3 out of 4 cases, thyroid administration aids in diagnosis in doubtful cases. Failure of the goiter to respond and failure of the radioiodine accumulation to be suppressed constitutes suggestive evidence for a diagnosis of hyperthyroidism.

The significance of single thyroid nodules is currently controversial. Some feel that all such nodules should be removed because 10 to 20 per cent of them are considered malignant at pathologic examination. Others feel that the death rate from carcinoma of the thyroid is so low that the likelihood of death from thyroid surgery is greater than that of saving a life from routine removal of thyroid nodules. The finding that single nodules often respond to thyroid indicates that their hyperplastic state is of a physiologic and not a neoplastic nature. Simple enlargement of the thyroid gland is generally accepted as functional hypertrophy. If only one lobe of the gland is enlarged, this is also accepted as functional hypertrophy, even though the other lobe is completely normal in size. It is usually assumed that one lobe is more sensitive to thyrotropin than the other. In any event, thyroid therapy seems to be as beneficial in unilateral thyroid enlargement as in bilateral. It is possible that a single nodule represents a localized area which has a lower thyrotropin threshold than the rest of the gland; the response of the nodules noted in this series, not greatly different from that of other types of goiter, lends support to such an hypothesis.

SUMMARY

A review has been made of the treatment of simple goiter with thyroid since the inception of such therapy in 1894. In addition, 50 cases treated during a five-year period are reported. Seventy-six per cent of the patients responded to therapy with a decrease in the size of the goiter and 40 per cent had a complete remission. Only 2 relapses were observed during the one to seven years of observation following treatment. Although it is anticipated that more will occur in the future, such relapses should be amenable to another course of thyroid therapy.

Eighty-seven per cent of 23 diffuse goiters responded to therapy, 44 per cent undergoing complete remission. Sixty-seven per cent of 9 multinodular goiters had a favorable response, 33 per cent disappearing completely. Sixty-seven per cent of 18 single nodules responded and 39 per cent disappeared completely. Only 15 per cent of 40 goitrous patients not treated with thyroid had a reduction in the size of the goiter.

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ACTH AND CORTISONE THERAPY OF ACUTE NONSUPPURATIVE (SUBACUTE) THYROIDITIS*†

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ACUTE nonsuppurative (subacute) thyroiditis is an acute febrile disorder. Characteristically, there is pain referable to the thyroid, with tenderness and swelling of the gland. Systemic symptoms of febrile disease may be marked and may overshadow the local manifestations. The etiologic agent remains obscure and no cure is known. Dramatic relief has recently been reported by Crile (1) and by Clark and associates (2) to follow ACTH and cortisone therapy. Crile treated four patients and Clark three.

The present report presents the experience of this clinic with these agents. The study was initiated as a consequence of the finding of Werner, Hamilton and Frantz (3) that ACTH and cortisone produce definite clinical and histologic changes in chronic thyroiditis of the Hashimoto type (struma lymphomatosa). Immediate and dramatic relief of both systemic and local symptoms and signs were noted in the first patient with acute thyroiditis so treated (Fig. 1). Unfortunately it became evident that relief, and not cure was being effected (Fig. 2). It therefore became necessary to determine if these agents influenced adversely the development of the spontaneous remission (Fig. 3) which generally terminates the disease. No such inhibition of recovery has been apparent (Fig. 4); therefore, this form of therapy can be recommended for use.

There were 6 patients in the present series, all with classic acute nonsuppurative thyroiditis. Confirmatory evidence in the laboratory included a high sedimentation rate and a greatly reduced thyroidal uptake of I^{131} in twenty-four hours, as previously described by us in this condition (4). There were 2 men and 4 women. One additional female patient has been included in order to demonstrate the tendency of the disease to terminate abruptly, (Fig. 2).

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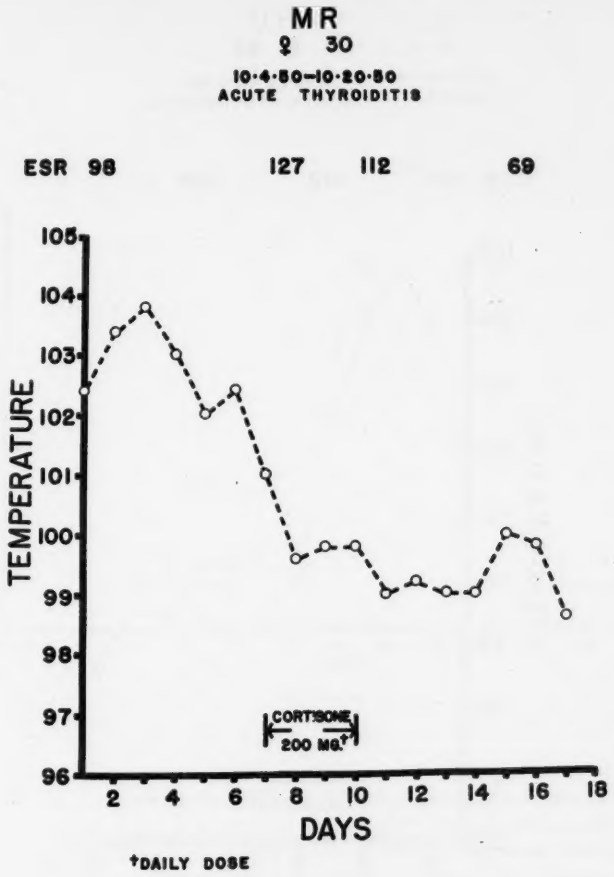

FIG. 1. Case 1.

ACTH[1] or cortisone was given every six hours, according to varying dosage schedules (Table 1). Subsidence of temperature, loss of tenderness of the gland with beginning decrease in size, and restoration of a sense of well-being followed within twelve to twenty-four hours of the use of ACTH. The same effects appeared within forty-eight to seventy-two hours after beginning cortisone.

Sustained remission followed cessation of therapy in 2 patients given a short course of treatment. Recurrence of symptoms or fever, or both, was noted in 4 subjects. In 1 of the 4, it was possible to renew and maintain

[1] Supplies of ACTH were received through the courtesy of Armour & Co.

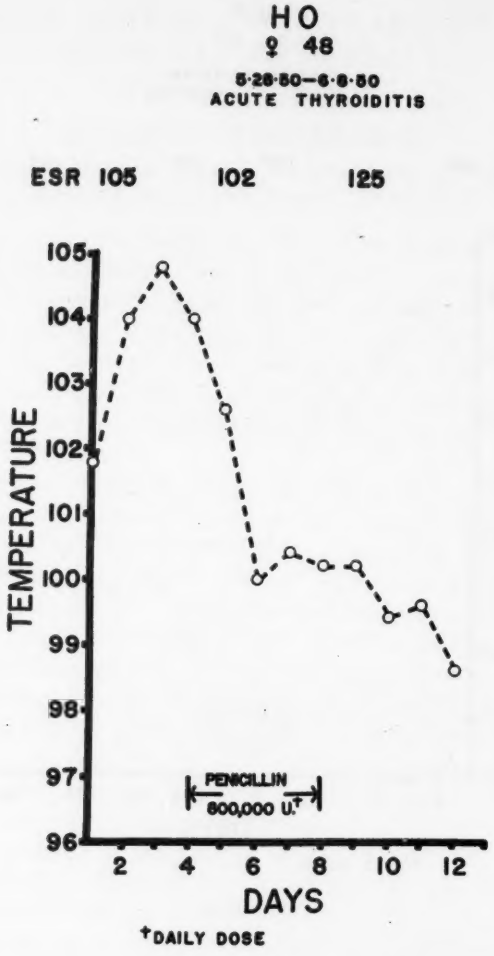

FIG. 2. Case 7.

therapy for three weeks; upon ultimate withdrawal of the hormone after this time, the patient remained well (Fig. 4). Follow-up observations for one to twelve months on all patients revealed no apparent adverse effect from the treatment. All patients became euthyroid and their thyroid glands returned to normal size.

ABSTRACTS OF CASE HISTORIES

Case 1 (Fig. 1). M.R., female, aged 32. UH#943093—Admission: Oct. 4, 1950. Discharge: Oct. 20, 1950.

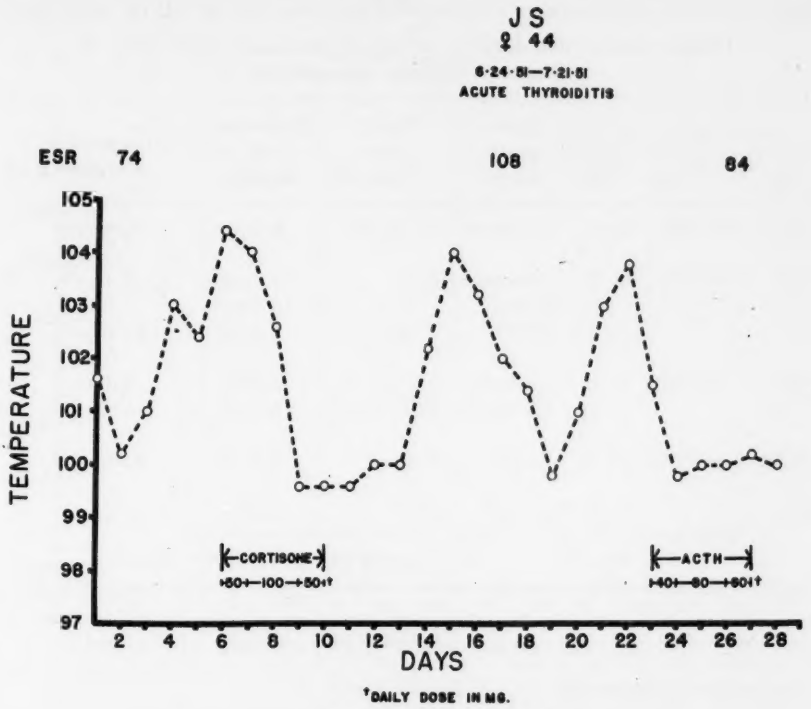

FIG. 3. Case 2.

Admission was for anterior neck pain radiating to the angle of the jaw on the left and to the left ear, of three weeks' duration. Fever and dysphagia were noted at the onset and, after a few days, enlargement of the thyroid. For four days before admission, mild arthralgias, diminished hearing and chilliness were noted. The patient fainted the morning of admission. Previous history and illnesses were irrelevant. Physical examination was noncontributory, apart from diffuse enlargement of the thyroid to three to four times normal size, and extreme tenderness of the gland.

Essential laboratory findings were: WBC 14,800 with PMN 74 per cent; sedimentation rate 98–125 mm. at one hour; BMR+15 per cent and later, +20 per cent; fasting serum cholesterol level 147 mg. per 100 cc.; and thyroidal I^{131} uptake at twenty-four hours, zero (per cent).

Cortisone administration was begun five days after admission, in a dosage of 25 mg. intramuscularly every six hours. After twenty-four hours, this was increased to 50 mg. every six hours for the next three days. The thyroid became nontender and the temperature fell to normal by forty-eight hours after the last injection. The patient felt "cured." Subsequent to cessation of treatment, she remained well. Three weeks after discharge the uptake of I^{131} was 27 per cent at twenty-four hours. The thyroid was still palpable two months after discharge, but was normal by four months after discharge.

Case 2 (Fig. 3). J.S., female, aged 44. UH#050586—Admission: June 24, 1951. Discharge: July 21, 1951.

TABLE 1. ACUTE NONSUPPURATIVE THYROIDITIS TREATED WITH ACTH OR CORTISONE

Dosage schedule and duration of induced remission before return of symptoms and signs in 6 patients.

Patient	U. Hosp. No.	Age & Sex	Therapeutic agent	Daily dose (Gm.)	Duration of therapy	Duration of remission
M.R.	943093	32 F	Cortisone	0.1–0.2	4 days	Sustained
J.S.	050586	44 F	Cortisone	0.1	4 days	5 days*
			None	—	15 days	—
			ACTH	0.06	4 days	10 days
R.G.	767387	48 F	Cortisone	0.15	5 days	5 days
			Cortisone	0.05–0.2	8 days	5 days
A.W.	058591	43 M	ACTH	0.1	3 days	Sustained
S.R.	†	44 M	ACTH	0.1	4 days	3 days
A.W.	450326	47 F	ACTH	0.02–0.08	8 days	Recurrence on lowering dosage to 0.02 Gm. level.
				0.015–0.08	12 days	Sustained

* Spread to opposite lobe.

† Courtesy Dr. Leo Morgenstern, White Plains Hospital, New York.

Admission was for sharp intermittent pain behind the right ear and in the lower anterior neck of one week's duration, associated during the last day with a fever of 102° F. The only known sore throat had been noted three months previously. The past history and illnesses were noncontributory. Physical examination revealed nothing abnormal, except for a small thyroid, definitely tender on the right.

Essential laboratory findings were: WBC 18,160 with PMN 76 per cent; sedimentation rate 74–108 mm. at one hour; BMR +18 per cent; fasting serum cholesterol level 290 mg. per 100 cc.; and thyroidal I^{131} uptake at twenty-four hours 13 per cent (on entry, with right lobe involvement only), then 3 per cent sixteen days later (upon involvement of left lobe as well).

Cortisone therapy was begun five days after entry, in a dosage of 25 mg. intramuscularly every six hours for four days. The temperature fell after forty-eight hours and the thyroid gland became smaller and nontender. The patient felt completely well. Symptoms recurred five days after the last injection, with apparent additional involvement of the left lobe of the gland. Nine days after the last cortisone injection, ACTH was administered intramuscularly in a dosage of 10 mg. every six hours the first day, and then 20 mg. every six hours for the next three days. Twelve hours after the start of therapy, the same dramatic relief ensued as with cortisone. However, symptoms and signs recurred ten days after discontinuing this treatment. The patient was given x-ray therapy to the gland, with recovery two weeks later. She was apparently euthyroid and well four months later.

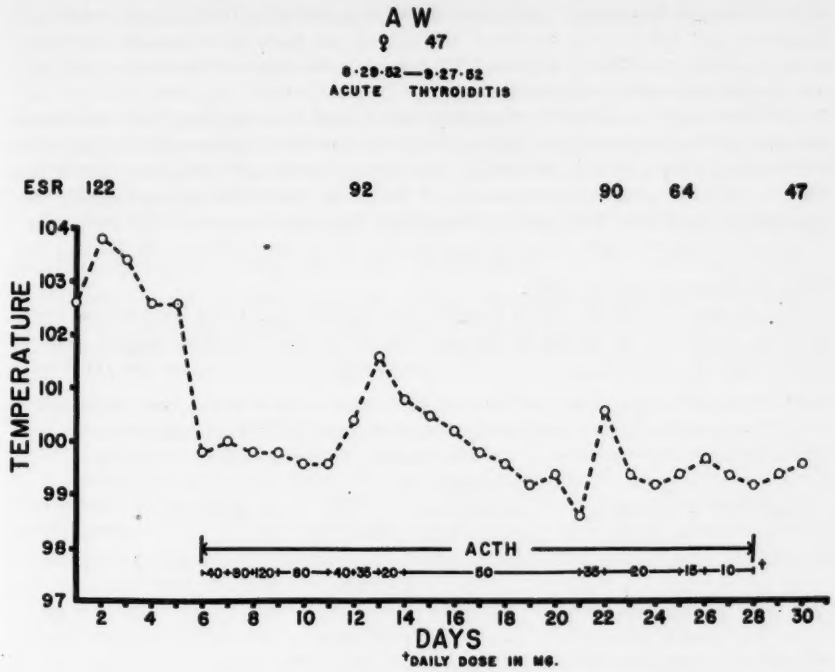

FIG. 4. Case 6.

Case 3. R.G., female, aged 48. UH#767387—Admission: June 25, 1951. Discharge: July 27, 1951.

Admission was because of five weeks of pain in the thyroid region, starting one week after an upper respiratory infection. The history was otherwise irrelevant. Physical examination was noncontributory, except for a diffusely swollen, tender, firm thyroid.

Essential laboratory findings were: WBC 9,100, with PMN 33 per cent; sedimentation rate 49–97 mm. at one hour; BMR +12 per cent; and thyroidal I^{131} uptake, 7 per cent at twenty-four hours.

The patient was given propylthiouracil for one week. No effect on the thyroiditis was observed. Cortisone was then given in a dosage of 25 mg. intramuscularly every six hours for five days. By forty-eight hours, the gland was nontender and the patient was asymptomatic. Five days after the last injection, there was a return of all symptoms and signs. Complete relief in forty-eight hours again followed cortisone therapy during the next eight days, but relapse was evident five days after stopping this treat nent. X-ray therapy was given and the patient was well one month later and has stayed well. She is now euthyroid one year later and has a normal sized gland.

Case 4. A.W., male, aged 43. UH#058591—Admission: August 25, 1951. Discharge: September 8, 1951.

Admission was because of a sore throat of five weeks' duration, despite antibiotic therapy. The rest of the history was noncontributory. The physical examination showed nothing abnormal apart from the thyroid, which was diffusely swollen and exquisitely

tender. Essential laboratory findings were: WBC 8,200, with PMN 54 per cent; sedimentation rate 105 mm. at one hour; BMR +25 per cent; serum precipitable iodine level 12 gamma per 100 cc.; thyroidal I^{131} uptake at twenty-four hours zero (per cent) and oral glucose tolerance curve, diabetic.

ACTH therapy was given for three days in a dosage of 25 mg. every six hours intramuscularly. There was complete relief of symptoms and loss of tenderness of the gland by twelve hours after onset of treatment. The patient continued well after cessation of therapy, and had progressive shrinkage of the gland. At follow-up, one month after discharge, a small hard lobe was felt bilaterally. The patient was well and euthyroid.

Case 5. (Courtesy, Dr. L. Morgenstern). S.R., male, aged 44. Admission: July 27, 1951. Discharge: August 8, 1951.

Admission to the White Plains Hospital was for sore throat and fever of one week's duration, unrelieved by antibiotic therapy. Headache and fever were present from the onset. Three days before admission, the thyroid region had become swollen and tender.

TABLE 2. RESULTS OF TESTS OF THYROID FUNCTION IN 3 OF 6 PATIENTS WITH ACUTE NONSUPPURATIVE THYROIDITIS TREATED WITH ACTH OR CORTISONE

Patient	Date	Thyroidal 24-hour I^{131} uptake (%)	SPI (γ/100 cc.)	BMR %	Cholesterol (mg./100 cc.)
M.R.	Oct. 5, 1950	0	7.5	−15	147
	Oct. 12	0		− 2	147
	Oct. 17	0	12.0	− 0	
	Nov. 22	27			
J.S.	June 30, 1951	13	10.7	−18	
	July 6		9.8		
	July 10	3	9.6		
	July 13		8.9		
	July 17		8.5		
	July 20		6.7		
A.W.	Sept. 4, 1952	2	7.2	− 9	
	Sept. 12	3	8.8		
	Sept. 19		9.2		
	Sept. 26		5.7	−27	243
	Oct. 27			−15	

Definite bilateral thyroid enlargement and tenderness were observed on examination. The remainder of the history and physical examination was noncontributory.

Propylthiouracil, 0.025 to 0.05 Gm. three times daily for three days had been unavailing. ACTH therapy was begun in a dosage of 25 mg. every six hours intramuscularly for four days. The patient became and remained afebrile and asymptomatic after twelve hours. There was abrupt loss of tenderness of the gland, which became much smaller and harder in the two days after cessation of therapy. However, one day later all symptoms and signs recurred, to disappear spontaneously two weeks later without further therapy other than aspirin. The patient has remained well and euthyroid since.

Case 6. (Fig. 4). A.W., female, aged 47. UH#450326—Admission: August 29, 1952. Discharge: September 27, 1952.

Admission was for malaise, dysphagia, fever and fatigue, of one month's duration. The patient's neck had become swollen and tender one week after onset. Cough and night sweats had been present for the week before entry. The history was otherwise noncontributory. Physical examination showed nothing abnormal, except for bilateral tender enlargement of the thyroid, greater on the right. A lymph node superior to the left thyroid lobe was palpable.

Essential laboratory findings were: WBC 13,500, with PMN 71 per cent; sedimentation rate 122 mm. at one hour; BMR −9 per cent; and thyroidal I^{131} uptake 2 per cent at twenty-four hours.

Therapy with ACTH was begun after six days of spiking temperature, in a dosage of 20 mg. every six hours intramuscularly. There was immediate flattening of the temperature curve, with complete symptomatic relief within twelve hours. After five days the daily dose of ACTH was reduced each day over a period of three days, followed by a recrudescence of temperature and return of symptoms on the third day. This was the day when a total of 20 mg. of ACTH was given. Dosage was raised to 25 mg. every six hours intramuscularly for eight days. Then, dosage was reduced a second time to 10 mg. every twelve hours and, after two days, to 5 mg. every twelve hours for two days. At this time treatment was discontinued, and the thyroid gland was found to be palpable, nontender and very firm on the right, but nonpalpable on the left; it was considerably smaller than at beginning of therapy. The patient felt well. Six months later she was still euthyroid and well, with a normal sized gland.

Case 7 (Fig. 2). H.O., female, aged 48. UH#999528—Admission: May 28, 1950. Discharge: June 8, 1950.

This patient is included in the present series to illustrate the tendency for the disorder to subside abruptly and spontaneously. She was admitted for severe sore throat and fever of nineteen days' duration. The neck had been swollen and tender in the thyroid area for fourteen days before entry. Dysphagia, night sweats, anorexia and temperatures up to 104° F. had been present. Physical examination revealed little of significance, except a bilaterally firm, moderately large, tender thyroid with an adjacent palpable cervical lymph node.

Essential laboratory findings were: WBC 14,600, with PMN 71 per cent; sedimentation rate 105–125 mm. at one hr.; BMR −1 per cent; fasting serum cholesterol concentration 156 mg. per 100 cc.; and thyroidal I^{131} uptake 7 per cent at twenty-four hours.

The patient was given procaine penicillin-G in a dosage of 800,000 units daily subcutaneously. After two days, the fever had abated. Five days later the patient was well, with a thyroid gland which was obviously decreasing in size.

DISCUSSION AND CONCLUSIONS

ACTH or cortisone therapy in acute nonsuppurative thyroiditis results in dramatic relief of the systemic and local symptoms and signs. The therapy does not appear to interfere with the spontaneous recovery which characterizes the disorder. This conclusion has been documented in 3 of the 6 patients in the present series. The 3 patients of Clark *et al.* continued well after cessation of therapy given for fourteen days or longer. Two of Crile's patients were treated only briefly; detailed information is lacking with regard to the other 2. but apparently they did well.

The level of ACTH or cortisone dosage should be kept as low as is consistent with a therapeutic effect, to avoid risk of the complications caused by these agents. Efforts to reduce dosage should be made periodically and treatment should be stopped when it appears that remission has supervened. It should be remembered that the disease may last twelve weeks or more before spontaneous remission occurs.

Careful follow-up observations of all treated patients should be made in respect to possible prolongation of the course of the disease consequent to the use of ACTH or cortisone, and in respect to possible increased incidence of chronic thyroiditis subsequently. Limited follow-up studies on the 6 patients in the present series have indicated complete return of normal thyroid health and function.

SUMMARY

1. ACTH or cortisone was given to 6 patients with acute nonsuppurative thyroiditis.

2. Abrupt cessation of symptoms and relief of tenderness of the thyroid occurred within twelve hours of the start of ACTH therapy and within forty-eight hours of the beginning of cortisone therapy.

3. ACTH or cortisone therapy does not prevent the development of the spontaneous remission which customarily ends the disease process. Three of the 6 patients showed a remission while being treated.

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THE PHYSIOLOGIC ACTIVITY OF *l*-TRIIODOTHYRONINE*

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IN a previous communication dealing with the physiologic activity of various analogues of thyroxine, Lerman, Harington, and Means (1) pointed out that any change in the structure of the thyroxine molecule resulted in a compound with activity less than that of *l*-thyroxine. It is, therefore, not surprising that the reports by Gross and Pitt-Rivers (2) of a compound, *l*-triiodothyronine, with biologic activity greater than that of *l*-thyroxine aroused a good deal of interest. When this material became available,[1] its biologic effect was observed in several patients with myxedema. It is the purpose of this paper to report on the activity of *l*-triiodothyronine in humans and also on its effect in certain phases of iodine metabolism.

METHOD AND MATERIAL

The compound, 3,5,3′-*l*-triiodothyronine, was assayed in 4 patients with myxedema. The material was administered daily in dosage of 0.1 mg. intravenously and the resulting changes in the basal metabolic rate were compared with those observed in our standard assays of thyroxine polypeptide (1.0 mg. by weight—0.5 mg. of iodine) or of *l*-thyroxine (0.4 mg. by weight—0.25 mg. of iodine). In 2 of these patients the serum protein-bound iodine level was determined before, during and after the assay. In the third patient, at the start of the metabolic assay, the effect of a single dose of 0.1 mg. of *l*-triiodothyronine on the serum protein-bound iodine concentration and on the urinary excretion of iodine was compared with the effect of 0.42 mg. of *dl*-thyroxine. In a fifth patient, in whom no basal metabolic assay was made, the effect of 0.2 mg. of *l*-triiodothyronine was compared with that of 0.2 mg. of *l*-thyroxine on the protein-bound iodine level and on the urinary excretion of iodine.

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[1] We are indebted to Dr. A. E. Heming of Smith, Kline and French Laboratories for a supply of this material which they obtained from the Glaxo Laboratories, where it was synthesized.

RESULTS

The results of the assay of *l*-triiodothyronine on the 4 patients with myxedema are shown in Figure 1. Patient A. G. gave a standard response at the daily intravenous dosage level used—0.1 mg. The response of Patient A. D. was apparently greater than standard during the first part of the assay, but this may be disregarded because the patient was running a fever as a result of infected leg ulcers. As the temperature subsided by the

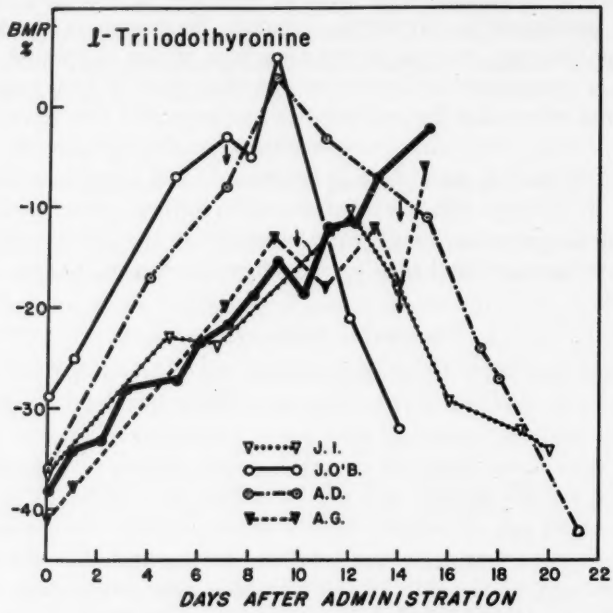

FIG. 1. The calorigenic response of 4 patients with myxedema to the daily administration of 0.1 mg. of *l*-triiodothyronine intravenously. The solid black line represents our standard curve of response to the administration of *dl'*-thyroxine polypeptide in a dosage of 0.5 mg. of iodine daily. Small arrows indicate day of final dose.

twelfth to thirteenth day, the level of metabolism approached the standard. The assay on Patient I. J. was stopped after ten days because of the onset of substernal pain; the response was standard up to that point. The response of the fourth patient, J. O'B., was definitely greater than standard, so that the triiodothyronine had to be omitted after seven doses. However, in evaluating this assay one should bear in mind the fact that the initial basal metabolic rate level of −29 per cent was higher than that of the other 3 patients and of the standard curve. It may, therefore, be inferred that the activity of *l*-triiodothyronine is four to five times as great

TABLE 1. CHANGES IN SERUM PROTEIN-BOUND IODINE LEVEL IN 3 PATIENTS WITH MYXEDEMA RECEIVING 0.10 MG. OF *l*-TRIIODOTHYRONINE DAILY

Patient	Protein-bound iodine (gamma per 100 cc.)		Time after last dose (hrs.)	No. days of treatment
	Before treatment	After treatment		
A.G.	0.3	0.3	36	14
A.D.	1.0	0.6	18	14
J.O'B.	1.3	0.6	16	7

as that of *l*-thyroxine in terms of weight, and six or more times in terms of iodine.

The clinical effects and the changes in the blood cholesterol concentration produced by *l*-triiodothyronine were of the same order of magnitude as those produced by thyroxine. However, the effect on the protein-bound iodine concentration was different. As shown in Table 1, the protein-bound iodine level in 3 of the patients in whom it was assayed dropped to the pretreatment level within sixteen to thirty-six hours after the last dose. In patients receiving thyroxine the protein-bound iodine level remains in the euthyroid range of 5 to 7 gamma per 100 cc. for several days after omission of the hormone. The difference in the effect of triiodothyronine and thyroxine on the blood iodine concentration is also shown in Table 2. Here, over a 24-hour period, the effect on the protein-bound iodine level of a single dose of triiodothyronine is compared with the effect of a single

TABLE 2. RANGE OF SERUM PROTEIN-BOUND IODINE AND URINARY EXCRETION OF IODINE IN 2 PATIENTS WITH MYXEDEMA FOLLOWING SINGLE INJECTIONS OF TRIIODOTHYRONINE OR THYROXINE

		Protein-bound iodine (gamma per 100 cc.)			Urinary I_2 (gamma/24 hrs.)
		Control	6 hrs.	24 hrs.	
A.D.	0.1 mg. *l*-triiodothyronine;	1.0	1.3	1.2	250
	0.42 mg. of *dl*-thyroxine	0.7	2.7	2.0	166
M.I.	0.2 mg. of *l*-triiodothyronine;	0.3	1.0	0.2	79
	0.2 mg. of *l*-thyroxine	0.0	2.3	1.5	104

dose of thyroxine in 2 patients. In one case 0.1 mg. of *l*-triiodothyronine is compared with 0.42 mg. of *dl*-thyroxine; in the other, 0.2 mg. of *l*-triiodothyronine is compared with 0.2 mg. of *l*-thyroxine. It will be noted that after the administration of *l*-triiodothyronine there was little or no change in the protein-bound iodine level observed for twenty-four hours, whereas after doses of thyroxine of lesser physiologic activity but of equal or greater weight, there was an appreciable rise.

The excretion of iodine in the urine was measured for twenty-four hours in these 2 patients during the same period in which changes in the blood iodine were being observed, after single doses of triiodothyronine and thyroxine. The results failed to explain the variations in blood iodine concentration. In the first case the excretion was considerably greater after 0.1 mg. of *l*-triiodothyronine than after 0.42 mg. of *dl*-thyroxine; in the second case it was somewhat less after 0.2 mg. of *l*-triiodothyronine than after an equal amount of *l*-thyroxine.

In 3 of the patients in whom an assay was made, as shown in Fig. 1, the drop in basal metabolism was followed after omission of triiodothyronine. In all of these patients the basal metabolic rate reached the pretreatment level in from seven to nine days after omission of the hormone. This is in marked contrast to the change in metabolism observed when a hypothyroid patient, treated with thyroid or thyroxine, stops medication. The slow drop in metabolism over a fifty- to seventy-day period represents the "decay curve" of thyroxine as described by Means and Lerman (3), and by Thompson *et al.* (4).

DISCUSSION

As indicated before, the report by Gross and Pitt-Rivers of the high degree of physiologic activity of triiodothyronine was most surprising. The data presented here confirm their findings. In human myxedema, *l*-triiodothyronine is from four to five times as active as *l*-thyroxine. Qualitatively, the clinical effects produced by these two compounds are about the same, but the time factors are different. According to Rawson (5) a single large dose of triiodothyronine produces a rise in metabolism sooner than an equivalent amount of thyroxine, and the metabolism reaches a peak sooner with triiodothyronine than with thyroxine. Similarly, the drop in metabolism following omission of triiodothyronine, as just reported, is much faster than after omission of thyroxine. Although the clinical picture, as observed from day to day with the administration of daily doses of triiodothyronine, may change the same way as with daily doses of thyroxine, some aspects of it may be altered more rapidly by triiodothyronine than by thyroxine. For example, the abnormal electrocardiographic pattern, consisting of flat or inverted T waves in all leads, reverted to normal

after only six doses of triiodothyronine in one patient and after ten doses in another. In the study of the "Heart in Myxedema" by Lerman, Clark, and Means (6) several instances are cited in which the abnormal components of the electrocardiogram reverted to normal only after weeks or months.

For many years it has been claimed that since *l*-thyroxine is the most active iodine-containing amino acid, and since it occurs naturally in the thyroid, it must therefore be the active thyroid hormone. Now that *l*-triiodothyronine is known to be more active than *l*-thyroxine, it is only natural to assume that it is the active hormone. In this connection the rapid clearing of triiodothyronine from the blood after prolonged administration, and the failure of single doses of triiodothyronine to raise the level of the serum protein-bound iodine appreciably, are of interest. They suggest that triiodothyronine leaves the extracellular spaces rapidly to enter the tissue cells, thus accounting for the rapid rise in metabolism observed. The precipitous drop in basal metabolism after the omission of triiodothyronine, suggests that triiodothyronine disappears rapidly from intracellular fluid also. The finding, in one case reported here, of a high excretion of iodine in the urine after a single dose of triiodothyronine, would tend to confirm this idea. These observations, plus the fact that blood and tissue normally contain only small amounts of triiodothyronine, lend additional support to the concept that triiodothyronine is the active thyroid hormone.

One may therefore visualize the normal thyroid hormone equilibrium as follows: the thyroid gland contains a large reservoir of thyroglobulin which serves as a source of thyroxine. As thyroglobulin is hydrolyzed, the thyroxine formed passes through the thyroid follicle into the blood stream, where it constitutes the major portion of organic iodine. The protein-bound iodine content of the blood is due to thyroxine and not to triiodothyronine. Here thyroxine becomes the reservoir for triiodothyronine. Thyroxine penetrates the cells of the end-organ and is converted to triiodothyronine. Once the latter is formed, it is utilized and cleared from the cells. In the conversion of thyroxine, two factors may operate to affect the rate: 1) the permeability of the cell to thyroxine may be poor, and 2) the degradation of thyroxine to triiodothyronine may be a slow process. Either one or both of these factors may explain the time lag in the action of thyroxine and also the slow "decay" curve of thyroxine.

Not all effects of thyroxine are overshadowed by those of triiodothyronine. The *in vitro* effect on the "efficiency of respiration" of a mitochondrial system, as measured by Lipmann (7), is greater with thyroxine than with triiodothyronine, although the oxygen consumption of such a system (Q_{O_2}) is greater with triiodothyronine. According to Lipmann the

greater permeability of cells to triiodothyronine as compared to thyroxine might explain its enhanced activity. Consequently, triiodothyronine need not be the thyroid hormone, and the presence of small amounts in tissue may be of no importance. Future investigations should throw more light on this problem.

SUMMARY AND CONCLUSIONS

1. *l*-Triiodothyronine, a normal but minor constituent of blood, thyroid, and other tissue, is from four to five times as active physiologically in human myxedema as *l*-thyroxine. The effect of triiodothyronine is more rapid than that of thyroxine; the return to the myxedematous state after omission of medication is more rapid with triiodothyronine than with thyroxine.

2. A single dose of *l*-triiodothyronine fails to change the protein-bound iodine level of the blood appreciably. After repeated doses triiodothyronine is rapidly cleared from the blood, so that within sixteen to thirty-six hours after the last dose, the protein-bound iodine concentration is again at the myxedematous level.

3. Such factors as permeability may explain the more rapid utilization of triiodothyronine as compared to thyroxine.

4. It is suggested, but not proved, that thyroxine serves as a reservoir for triiodothyronine and that triiodothyronine, converted from thyroxine in the tissue cells, is the effective thyroid hormone.

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A RADIOIODINE TRACER STUDY OF THE FATE OF HUMAN THYROID AUTOTRANSPLANTS*

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THE regenerative and growth capacity of human thyroid parenchyma has long been assumed by analogy with the results of animal experiments and on grounds of clinical observations following thyroidectomy. With radioisotope tracer technic a more direct method of evaluating the growth potential of human thyroid tissue became available. By this method we have formerly shown that following so-called "total" thyroidectomy grossly indiscernible fragments of thyroid tissue inadvertently left *in situ* are at times capable of a detectable function (1). Similarly, under certain conditions a consistent and progressive increase can be demonstrated in the functional activity of very small amounts (as small as 200 mg.) of thyroid parenchyma remaining after radical subtotal thyroidectomy (2). In the present study we have sought to gather further information regarding the parenchymal regeneration of thyroid tissue by investigating the behavior of thyroid autotransplants. Although several recent accounts deal with similar inquiries in experimental animals (3–11), and sporadic references may be found to clinical observations concerning autotransplants in man (12), only 1 case report containing data on human material obtained with methods utilizing radioisotope technics has been encountered in the literature (13).

MATERIAL AND METHODS

The pertinent preoperative data in the 9 cases studied are summarized in Table 1. The cases fall into three groups of 3 cases each. Group I covers diffuse hyperplastic goiter (Graves' disease); Group II, toxic adenomatous goiter; and Group III, nontoxic adenomatous goiter. Four of the 6 patients with toxic goiter were prepared for their operation with iodine or iodine

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and ACTH; the other 2 received iodine and antithyroid drugs preoperatively. The period of study up to the time of the compilation of this report varied from seven to eighteen months.

TABLE 1. PREOPERATIVE CLINICAL DATA

Case No.		Sex & age	BMR (%)	Serum		I^{131}		Preop. medic.	Duration of study (mos.)
				Cholest. (mg./100 cc.)	PBI (μg./100 cc.)	Uptake (ct./sec.)	Excr. (%)		
Group I									
Graves' disease	1	F, 28	+78	72	22	25–31–23	10/96 hr.	I_T-ACTH	13
	2	F, 62	+74	55	23	16–21–13	23/48 hr.	ACTH	13
	3	F, 19	+52	139	—	—	—	I_T-Antithyr.	11
Group II									
Toxic adenoma	4	M, 30	+85	139	—	—	—	I_T-Antithyr.	18
	5	F, 47	+72	50	29	18–21–14	12/96 hr.	I_T-ACTH	13
	6	F, 62	+50	296	—	—	—	I_T	7
Group III									
Nontoxic adenoma	7	M, 30	+1	126	—	—	—	None	11
	8	F, 51	−2	143	—	—	—	None	14
	9	F, 54	+6	—	—	—	—	None	13

In all but 1 of the cases of toxic goiter (Groups I and II) radical subtotal thyroidectomy was performed with a technique that permitted the visualization of the entire retrothyroidal course of the recurrent laryngeal nerve and the identification of the parathyroid bodies. As a rule, in these cases one lobe was completely removed but a small amount of parenchyma was left on the opposite side (Fig. 1). In Cases 5 and 8 the entire gland was taken out. In Case 7 one lobe was resected and the other left intact. The position of the transplant in relation to the thyroid remnants, and the respective weights of the transplants and remnants (in round numbers), are diagrammatically represented in Figure 2.

In all cases the graft was placed on the side in which no thyroid parenchyma was left, and was imbedded in the upper half or third of the sternocleidomastoid muscle. The transplanted tissue was taken from the most representative portions of the resected gland, and consisted of slices 1.0–1.5 mm. thick and 4.0–6.0 mm. wide. These were implanted into individual pockets made in the muscle substance. The size of the transplants and remnants was estimated by weighing pieces of tissue cut from the removed portion of the gland, which were as similar in size and appearance to the transplants and remnants as could be ascertained by common judgment of the operating team. The margin of error in such estimates by matched weight is about ± 10 per cent.

Postoperatively, the patients were given no medication affecting thyroid function. Studies were begun as early as feasible (from ten to eighty-three

FIG. 1. Sketch of the typical operative result in all cases of toxic goiter, except Cases 5 and 8 (in which total thyroidectomy was performed). One lobe is completely removed but a small amount of parenchyma is left on the opposite side. The graft is placed on the side in which no thyroid parenchyma is spared.

days postoperatively) and were repeated at intervals of about ninety days thereafter. For the investigation of the activity of the transplant and the remnant, a dose of 25 microcuries of I^{131} was administered orally. The uptake of the isotope by the tissue rests, and its urinary excretion in ninety-six hours were determined. The details of the tracer technique used have been published elsewhere (1). Concurrently an evaluation was recorded of the patient's clinical status and other indices of thyroid function, namely the serum PBI and cholesterol levels and the basal metabolic rate.

RESULTS AND DISCUSSION

From previous experience (1) we have reason to believe that a count of 1 per second or over indicates the presence of functioning thyroid tissue. Counts between 1 and 6 per second obtained over intact glands are associated with various degrees of clinical hypothyroidism. In clinically euthyroid patients, counts over 6 are usually obtained. Since several factors connected with the counting technique are difficult to control, and since the number of cases under study was small, our findings were not entirely consistent. Nevertheless certain definite trends could be discerned with a good degree of certainty (Table 2 and Fig. 3).

In Group I evidence of activity was present in every case. The activity

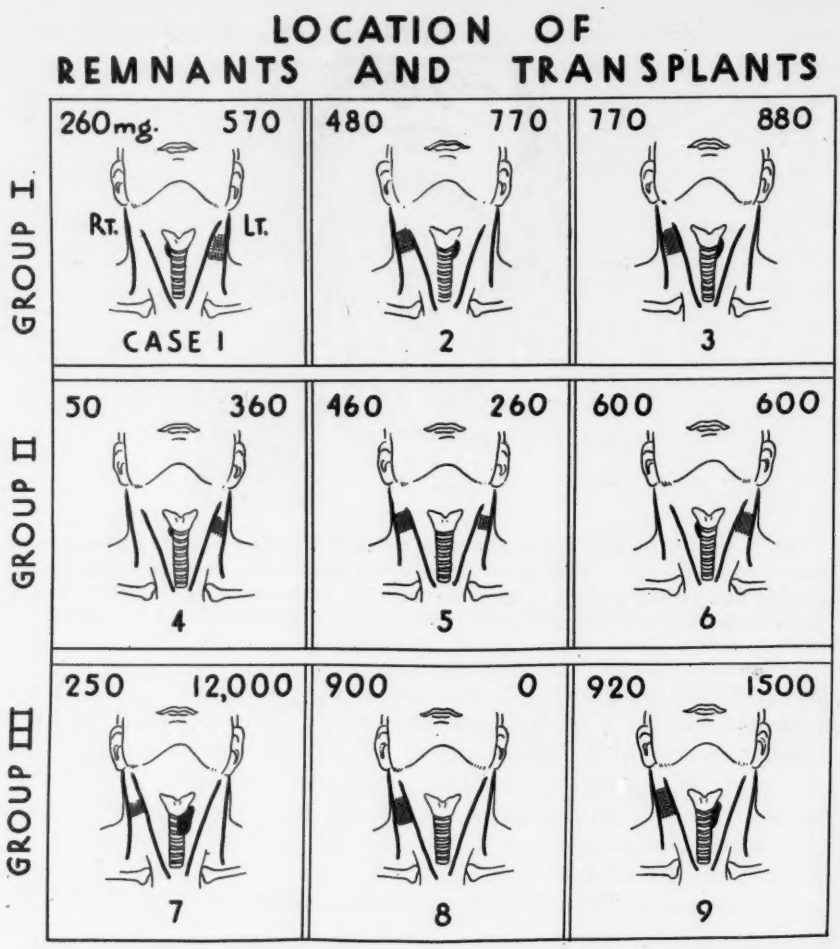

FIG. 2. The positions of the transplants and remnants, with their weights marked. In Cases 1, 2, 3, 4, 6 and 9 the variations of the characteristic arrangement shown in Figure 4 are represented. In Cases 5 and 8 the entire gland is removed. In Case 7 one lobe is resected and the other left intact.

seemed to be of a significant degree even at the time of the first postoperative study, except in Case 2. The increase was especially marked in Case 3. In Groups II and III activity was likewise present in every case, but occasionally it was detectable only after a longer postoperative interval. The increase in activity was of a lesser magnitude and at a slower rate.

It would be of great interest to attempt an analysis of the factors that

TABLE 2. I^{131} UPTAKE AFTER THYROIDECTOMY AND GRAFTING

Case No.	Transplant					Remnant				
	Size (mg.)	Counts per second				Size (mg.)	Counts per second			
		I	II	III	IV		I	II	III	IV
Group I										
1	570	2.4	1.4	8.5	6.5	260	4.6	2.0	6.0	11.5
2	480	0.3	2.0	6.8	2.7	770	0.6	1.4	6.2	4.2
3	770	1.6	22.0	34.5	30.4	880	2.8	4.0	31.0	17.8
Group II										
4	360	4.5	1.8	4.1	—	50	2.3	0.4	1.7	—
5	L260	0.4	1.0	7.2	1.6	0	—	—	—	—
	R460	0.6	1.6	6.4	2.7					
6	600	1.2	12.5	18.5	—	600	1.4	4.2	7.5	—
Group III										
7	250	2.2	1.4	3.5	—	12,000*	4.2	4.0	7.6	—
8	900	3.0	4.2	5.3	9.2	0**	0.4	0.6	1.5	3.7
9	920	0.6	1.2	3.5	—	1,500	1.6	3.6	20.8	—

* Estimate of entire lobe.
** See note for Fig. 3.

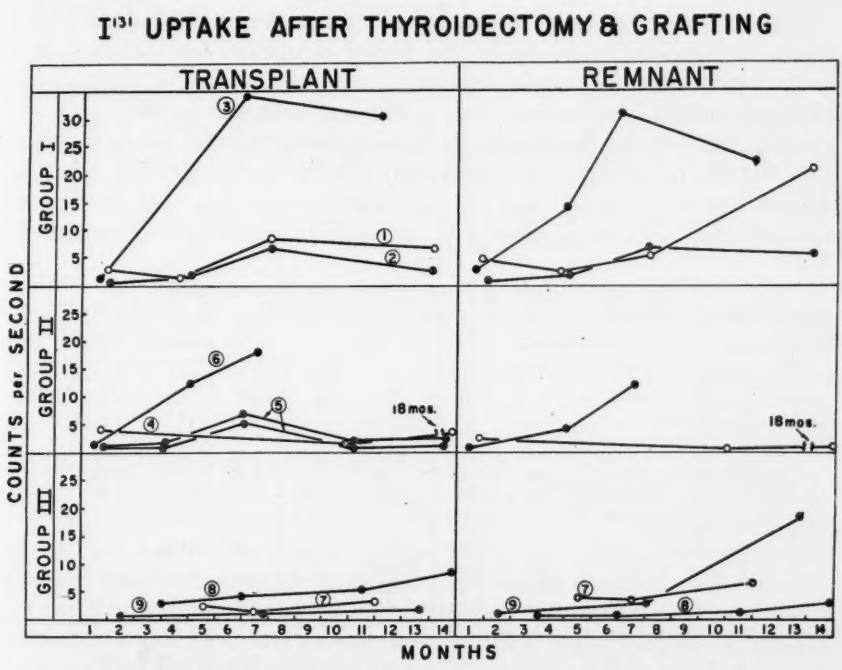

FIG. 3. Note: Although in Case 8 the thyroidectomy was meant to be total, a very small fragment (less than 100 mg.) of thyroid tissue had to be spared on the left, because of technical difficulties. As is not infrequently the case, this remnant assumed growth; hence the slight but definite evidence of activity on the side opposite the graft.

may determine the variations of uptake in the different cases. Since, however, because of the many variables, the cases are not strictly comparable even in groups, such an analysis must be somewhat speculative.

As regards the *tissue type* of the goiter in each group, the difference in behavior between Group I on the one hand, and Groups II and III on the other, appeared to be clear-cut. Thus thyroid tissue with diffuse hyperplasia displayed the greatest growth potentiality. The difference in activity between Groups II and III was, on the contrary, much less marked; but comparison involving so-called adenomatous thyroid tissue is fraught with special difficulties because of the confused state of our knowledge of the histopathology of the latter. In an attempt to eliminate the variable factor of size by estimating the uptake counts per 100 mg. of tissue, we obtained the same suggestive evidence regarding group differences (Table 3 and Fig. 4). It may be noted in this connection that tissue from hyperplastic goiter has been found to survive more readily than normal thyroid tissue, when transplanted to the anterior chamber of the eye of the rabbit (6).

With respect to the effect of the *time element* on the survival of the transplants, the general trend up to the period comprised by the sixth and seventh postoperative months was one of progressive increase in function, although a slight intermediate drop in iodine uptake was noted in Cases 1, 4 and 5. After the sixth and seventh postoperative months, the activity in all the cases in Group I (hyperthyroid) showed a mild decline, whereas the activity in Groups II and III continued to rise at a very slow pace. In short-term animal experiments (7, 11)—which are not quite comparable

TABLE 3. COUNTS PER SECOND PER 100 MG. OF TISSUE

Case No.	Transplant					Remnant				
	Size (mg.)	I	II	III	IV	Size (mg.)	I	II	III	IV
Group I										
1	570	0.42	0.24	1.49	1.14	260	1.77	0.77	2.30	4.42
2	480	0.06	0.42	1.41	0.56	770	0.77	0.18	0.80	0.55
3	770	0.17	2.44	4.50	3.95	880	0.42	0.21	3.55	2.02
Group II										
4	360	1.20	0.50	1.13	—	50	4.60	0.80	3.40	—
5	L260	0.15	0.38	1.15	0.62	—	—	—	—	—
	R460	0.13	0.34	1.00	0.59					
6	600	0.20	2.08	3.08	—	600	0.23	0.71	1.17	—
Group III										
7	250	0.88	0.56	1.40	—	12,000*	0.02	0.02	0.06	—
8	900	0.33	0.47	0.59	1.02	0**	—	—	—	—
9	920	0.70	0.13	0.38	—	1,500	0.05	0.10	1.39	—

* Estimate of entire lobe.
** See note for Fig. 8.

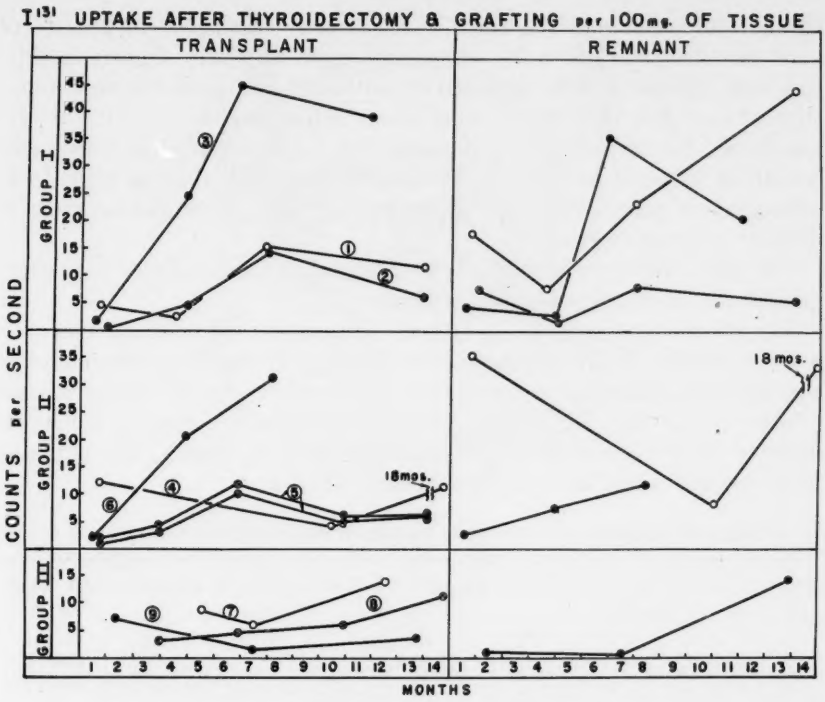

FIG. 4. Note: Regarding the curve of uptake of the remnant in Case 8, *see* note under Figure 3.

to the material here under discussion—thyroid autografts manifest an almost continuous ability to take up iodine, interrupted only by a brief period (four to six days) of inactivity at the time when the necrobiosis of the transplant is at its height and regeneration of the thyroid parenchyma has not yet progressed far enough (fifth to ninth days after grafting). The youngest graft in this study was ten days old when first investigated and it showed definite activity. Although one may postulate that the growth of the transplant will come to an end when it is capable of supplying the need of the organism for thyroxine, a longer follow-up will be necessary to determine whether the trends observed so far will be maintained.

On the assumption that a *systemic demand for thyroxine* is a necessary condition of the growth of a graft, the size of the transplant was originally made smaller than the calculated minimal requirement (the latter having been deduced from experiences with subtotal thyroidectomy (2)). There was no evidence among our findings to contradict this assumption but there were hints that other factors may be more important. One of these

factors undoubtedly is the tissue type, already discussed. In 2 cases of toxic adenomatous goiter the transplants grew only very slightly in thirteen and eighteen months respectively, although both patients were hypothyroid and thus their grafts must have been under the stimulus of systemic need for thyroxine. It is possible that the transplants in these cases contained tissue of intrinsically low growth potential, (having come from adenomatous goiters in which the functional state of component parts is difficult to appraise grossly).

The speculative possibilities of the influence of *hormonal factors* on graft growth are, of course, obvious and many.

The effect of the *patient's age* on graft survival cannot be assessed in such a small sample, but it may be significant that the most marked degree of regeneration occurred in a girl of 19 with a juvenile type of Graves' disease (Table 4 and Fig. 5.) In the seventh postoperative month, when the activity of the transplant apparently reached its height, the patient's graft became palpable and grossly visible (Fig. 6).

TABLE 4. PREOPERATIVE AND POSTOPERATIVE THYROID FUNCTION IN CASE 3

	BMR (%)	Serum		I^{131} Excr. (%/96 hr.)	I^{131} Uptake (ct./sec.)	
		PBI (μg./100 cc.)	Cholest. (mg./100 cc.)		Transpl. (770 mg.)	Remn. (880 mg.)
Preop.	+52	—	139	—	—	—
Postop. I	−12		261	77	1.6	2.8
II	−13	3.0	178	53	22.6	14.5
III	−10	4.0	160	70	34.5	30.1
IV	−13	—	160	—	30.4	17.8

Female, aged 19 yrs., with Graves' disease. Preoperative preparation: Tapazol and I_2. Period of study: eleven months.

As regards total thyroid function, postoperatively all the patients but one were euthyroid or mildly hypothyroid clinically (Table 5). All but one got along comfortably without replacement medication. The exception is the patient in Case 5, whose hypothyroidism is slowly progressing. The values for serum cholesterol and PBI concentrations, and for I^{131} excretion are in general agreement with the clinical classification of the patients, but the basal metabolic rates are in some instances (Cases 4 and 9) disproportionately low.

The changes in the functional state of the transplants and their corresponding parenchymal remnants were parallel, except when the respective sizes were markedly divergent. It may be pointed out that, based on

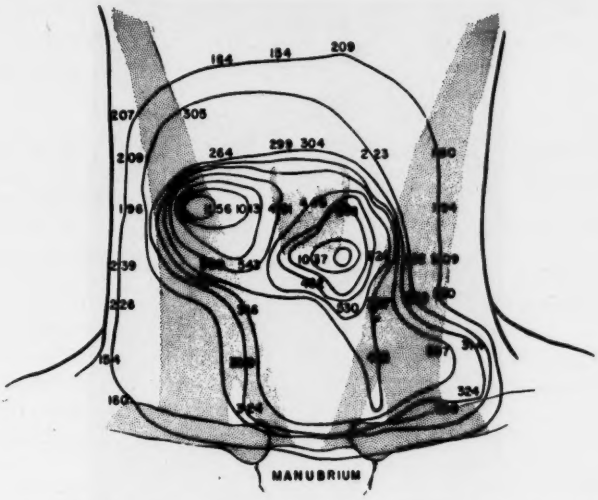

FIG. 5. Diagram of the contour scanning of the cervical region in Case 3 in the seventh postoperative month. There is a marked concentration of the circles connecting high counts over the site of the transplant and, to a lesser degree, over the site of the remnant.

observations mentioned at the outset (2), the amount of thyroid parenchyma preserved at operation in Cases 1, 3 and 4 was probably not by itself sufficient to maintain a euthyroid state. One may infer that in these cases the transplants furnished the additional amount of tissue needed for a normal degree of total thyroid function.

TABLE 5. PREOPERATIVE AND POSTOPERATIVE THYROID FUNCTION

Case No.	BMR (%)		Serum cholest. (mg./100 cc.)		I^{131} Excr. (% per 96 hr.)		Serum PBI (μg./100 cc.)		Postop. clinical state
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	
Group I									
1	+18	− 8	72	142	10	73	22.4	2.9	Euthyroid
2	+74	+ 2	55	320	23	68	21.7	2.1	Euthyroid
3	+52	−13	139	160	—	70	—	4.0	Euthyroid
Group II									
4	+85	−33	139	240	—	75	—	0.5	Sl. hypoth.
5	+72	− 7	50	259	12	70	29.4	1.5	Hypothyroid
6	+50	+ 4	296	296	—	65	—	4.9	Euthyroid
Group III									
7	+ 1	− 7	126	164	—	79	—	6.6	Euthyroid
8	− 2	−20	143	250	—	82	—	1.0	Sl. hypoth.
9	+ 6	−19	—	222	—	77	—	1.0	Euthyroid

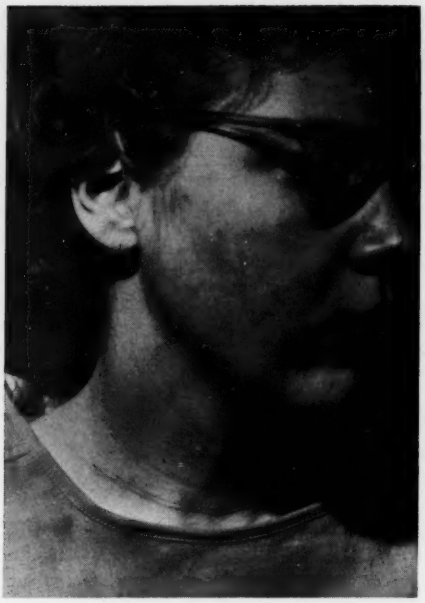

FIG. 6. The patient in Case 3 in the seventh postoperative month. A swelling is visible in the mid-third of the body of the right sternocleidomastoid muscle. This swelling was still visible and palpable as a circumscribed lump measuring about 2×2×1 cm., at the end of the eleventh postoperative month.

SUMMARY AND CONCLUSIONS

The clinical data and the results of radioiodine uptake and excretion studies are presented and discussed in 9 cases of subtotal and total thyroidectomy in which thyroid autografts have been made.

Slices of human thyroid parenchyma transplanted into the sternocleidomastoid muscle of the donor-host with a simple technique, show a consistent ability to survive.

The transplants may resume the specific physiologic function of accumulating iodine as early as ten days postoperatively—probably as soon as their vascular connections are established.

The functional activity of the transplants in terms of iodine uptake increases with time. This increase in activity is probably due, at least in part, to an actual growth of the grafts. The rate and magnitude of the increase in function are largely dependent on the tissue type of the transplant, grafts of hyperplastic goiter showing a decidedly greater growth potentiality.

The systemic demand for thyroxine and the age of the donor may be

among the factors influencing the survival and growth of the transplant.

Further observations are needed to ascertain the maximum limit of regeneration in the graft.

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THE THYROIDAL UPTAKE OF STABLE IODINE COMPARED WITH THE SERUM CONCENTRATION OF PROTEIN-BOUND IODINE IN NORMAL SUBJECTS AND IN PATIENTS WITH THYROID DISEASE*†

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THE uptake of radioactive iodine (I^{131}) by the thyroid gland has been shown, in general, to be in good agreement with the state of thyroid function (1). With gross alterations in the intake of stable iodine (I^{127}) and in patients who have received treatment for thyroid disease, the usual relationship between radioiodine uptake and thyroid function may be altered. Of particular clinical importance are the high radioiodine uptakes which have been noted in patients who have received radioiodine or surgical treatment for hyperthyroidism and who, by clinical and other laboratory criteria, are euthyroid (2). Conversely, normal radioiodine uptakes have been observed in treated patients who are still hyperthyroid (3). These findings could be explained either by 1) a disturbance in the orderly secretion of thyroid hormone of such a nature that iodine which is taken

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up by the gland is not released as circulating hormone, or 2) changes in the amount of stable iodine in extracellular fluid which is available for uptake by the thyroid gland, with the result that proportionately more or less of a dose of radioiodine is taken up by the thyroid gland than would ordinarily be the case at a given level of thyroid function. Our studies would support the latter hypothesis.

We have compared the radioiodine uptake with the protein-bound iodine concentration in two groups of individuals. One group was composed of normal subjects and patients with thyroid disease who had not received any therapy. The other group had been treated for hyperthyroidism with antithyroid drugs, surgery, or radioiodine, singly or in combination. The amount of stable iodine taken up by the thyroid gland has been estimated in some of these patients. In 4 instances, detailed studies to determine the significance of the stable iodine uptake have been performed. Finally, the amount of thyroid hormone which is utilized in the peripheral tissues at various serum concentrations of circulating thyroid hormone has been estimated.

MATERIALS AND METHODS

Patients studied have, for the most part, been referred because of some question of thyroid disease. Those in whom clinical and laboratory evidence excluded thyroid disease have been considered normal subjects. There is probably an increased incidence of borderline cases and also of patients who had received prior therapy for hyperthyroidism in the group studied. In all instances, no treatment had been given within three months of the study.

Tracer doses, usually 50 microcuries, of carrier-free I^{131} were given by mouth two to three hours after breakfast. The thyroidal uptake of radioiodine was determined at twenty-four hours and, when the turnover of radioactive iodine was expected to be rapid, also at six hours. Thigh counts were subtracted from neck counts if patients were monitored before twenty-four hours. Blood samples were drawn at the time of monitoring. Urine collections were entrusted to the patient and note made of any inadvertent losses. For radioactivity measurements in patients and in urine samples, a suitably shielded gamma-sensitive bismuth cathode Geiger-Mueller tube (Sylvania GG306) was employed. Counts in serum samples were made with a well-type scintillation counter. Duplicate measurements checked within 3 per cent.

For the chemical determination of stable iodine, the digestion-distillation method of Barker, somewhat modified (4), was used. Recovery of iodine was checked by measuring the radioactivity of samples before and after digestion and distillation.

The radioiodine uptake was expressed as the percentage of the dose (%), corrected for decay, which was measured in the neck. The stable iodine uptake was derived by multiplying the amount of stable iodine in the urine by the ratio of radioiodine uptake to radioiodine excreted in the urine during the period of observation (5). This was expressed as micrograms per hour (γ/hr.). The calculation is based on the assumption that the

specific activity of serum inorganic iodine equals the specific activity of urine inorganic iodine at any given moment and that the thyroidal and renal clearances of iodine remain constant, or at least in constant relationship to each other.

In 4 patients, additional observations were made at intervals during the first six hours. The rate of disappearance of radioactivity from the serum was determined by plotting percentage of dose per liter of serum (%/L) against time. The iodine space in liters (L) was calculated by dividing the percentage of the dose which had not appeared in the thyroid and in the urine by the percentage of the dose in the serum per liter (6). These calculations were made only for the interval following the dose before appreciable amounts of protein-bound iodine (as shown by measuring the radioactivity of the precipitated proteins) appeared in the serum.

Changes in the urinary iodine specific activity or the ratio of radioactive to stable iodine, expressed as percentage of dose of radioiodine per microgram of stable iodine (%/γ), were plotted against time after the dose. Serum total iodine concentration was measured directly as micrograms per 100 cubic centimeters ("γ%"). Serum inorganic iodine concentration was estimated by dividing the value for activity in the serum at the mid-point of the urine collection period by the value for the specific activity of the urine, and was expressed as micrograms per 100 cubic centimeters ("γ%").

Thyroidal and renal clearances were calculated by dividing the value for the percentage of the dose collected in the thyroid or in the urine by the interpolated value for serum radioiodine concentration at the mid-point of the collection period; the results were expressed as cubic centimeters per minute (cc./min.).

RESULTS

I. *Correlation between thyroidal radioiodine uptake and serum protein-bound iodine level*

The radioiodine uptake was compared with the protein-bound iodine concentration in two groups of individuals (Fig. 1). One group was composed of normal subjects and patients with thyroid disease who had not received any therapy. The other group was composed of patients who had been treated for hyperthyroidism with antithyroid drugs, surgery, or radioiodine.

In 85 patients who had not received prior treatment for thyroid disease, the radioiodine uptake showed a good correlation with the serum protein-bound iodine concentration ($r = .78$, p less than .01). Averages for the radioiodine uptakes at increasing levels of serum protein-bound iodine concentration showed a progressive increase until the hyperthyroid range was reached, where the radioiodine uptake was at a maximum. The range of uptake corresponding to each serum protein-bound iodine level was relatively narrow.

In 112 patients who had been treated for hyperthyroidism, there was often considerable discrepancy between the radioiodine uptake and the serum protein-bound iodine concentration, and a greater range of individual variation for each serum protein-bound iodine level, resulting in a lower correlation between the two values ($r = .53$, p less than .01).

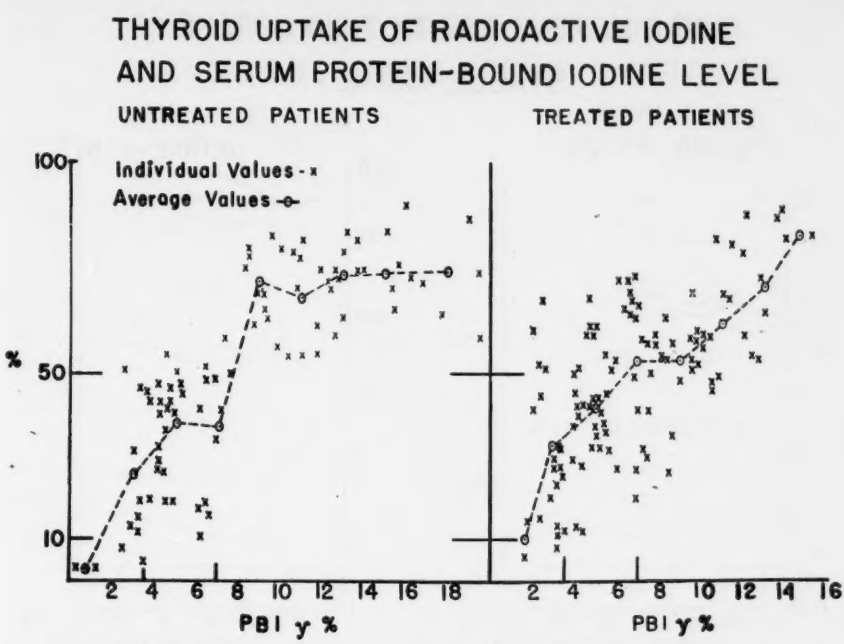

FIG. 1. The uptake of radioiodine by the thyroid gland (per cent) is plotted against the serum protein-bound iodine concentration (micrograms per 100 cc.). Normal values for the radioiodine uptakes are taken as 10 to 50 per cent, and for serum protein-bound iodine concentrations as 3.5 to 7.0 (micrograms per 100 cc.)

These findings were perhaps a result of a reduction in the storage of stable iodine in the thyroid gland following therapy. Without normal stable iodine storage capacity, there may be greater fluctuations in the amount of stable iodine in extracellular fluid, produced either by variations in dietary iodine or by changes in the amount of iodine released from the breakdown of thyroid hormone in the peripheral tissues, to which the radioiodine uptakes may be sensitive.

II. *Estimation of stable iodine uptake*

To correct for variations in the stable iodine content of extracellular fluid, the thyroidal uptake of stable iodine at different serum protein-bound iodine levels was estimated (Fig. 2). In 4 untreated, 2 euthyroid (SU, CO) and 2 hyperthyroid (MU, CS) patients, the stable iodine uptake was measured at two, four, six and twenty-four hours, in order to determine the effect of the time interval selected on the value obtained. The shorter the time interval, the more important would become errors in urine collection and in measuring thyroidal uptake. On the other hand,

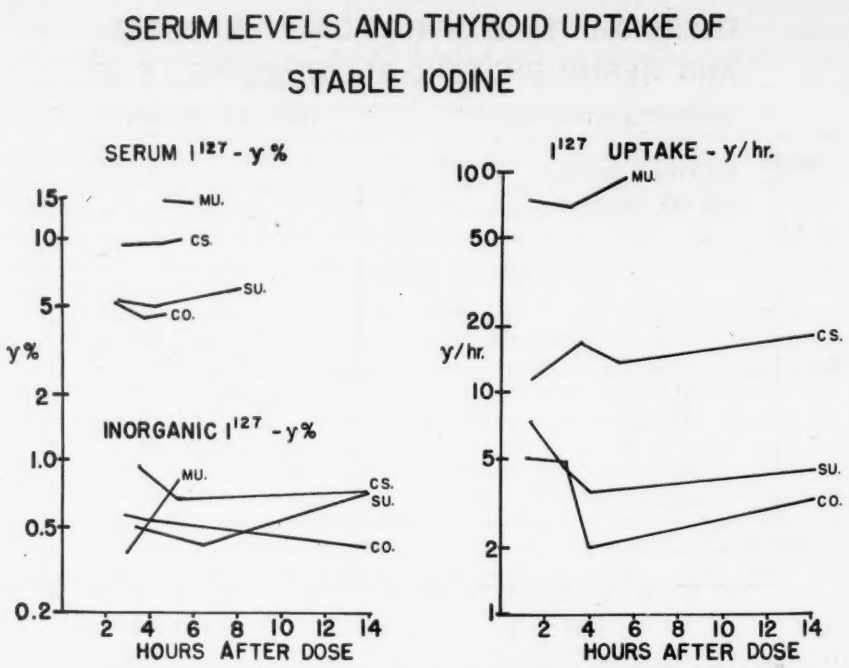

FIG. 2. Diurnal variations in the serum levels and the thyroidal uptake of stable iodine in 2 hyperthyroid patients (MU and CS) and in 2 euthyroid subjects (CO and SU) are plotted against the time in hours after a tracer dose of radioiodine.

prolongation of the interval beyond six hours would result in some loss of radioactivity from the thyroid gland as hormonal iodine, especially in patients with hyperthyroidism. Some variation might be expected aside from that induced by physiologic changes in thyroid clearance, renal clearance, and the serum inorganic iodine level from period to period. However, fluctuations in the calculated stable iodine uptake during a 24-hour interval were not as great as the differences between the stable iodine uptakes at the different levels of thyroid function, as indicated by the serum protein-bound iodine concentrations.

III. *Radioiodine clearances and the decrease in urinary iodine specific activity*

The changes in the iodine space, in the serum radioactive iodine concentration, and in the urinary iodine specific activity in these 4 patients were plotted against time after the dose (Fig. 3). There was a slight increase in the iodine space during the period of study, accounting for only a small fraction of the radioiodine leaving the serum. The major loss of radioiodine

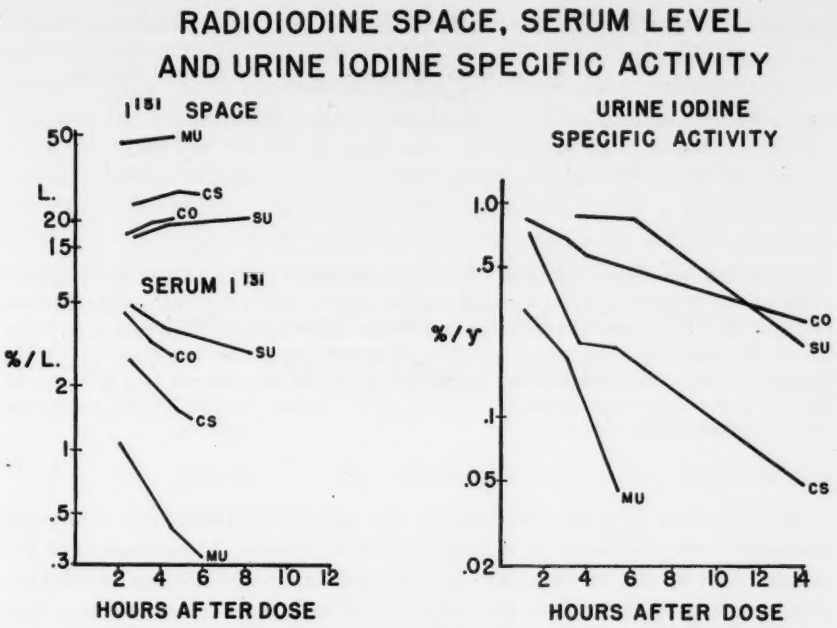

FIG. 3. In individual patients, the rate of fall in the serum radioiodine concentration (per cent of dose per liter) due to thyroidal uptake and renal excretion of radioiodine approximated the rate of decrease in urinary specific activity (per cent of dose per microgram), due to the addition of stable iodine to the extracellular iodide pool. There was little change in the radioiodine space.

from the serum was to the thyroid and the urine. The renal clearances in these patients were comparable, hence the main difference between patients to account for the difference in slope of the serum radioiodine concentrations was in the thyroid clearance (Table 1). In individual patients, the rate of fall in the serum radioiodine concentration, due to thyroidal uptake and renal excretion of radioiodine, approximated the rate of decrease in the urinary iodine specific activity due to the addition of stable iodine to the extracellular iodide pool after the ratio of radioiodine to stable iodine had reached its maximum value. This stable iodine increment was derived both from thyroxine metabolized in the tissues and from dietary iodine. Over an interval of time dietary iodine would equal urinary iodine excretion, hence a similar rate of fall in the serum radioiodine concentration and in the urinary iodine specific activity indicated an equilibrium between the thyroidal uptake of stable iodine and the thyroidal output and peripheral degradation of hormonal iodine.

TABLE 1

Patient	Renal clearance (cc./min.)	Thyroid clearance (cc./min.)
MU	39	252
CS	50	32
CO	30	12
SU	16	7

Renal clearances were calculated from the percentage of the dose in the urine divided by the percentage of the dose per liter of serum at the mid-point of the collection period and by the time of the collection in minutes; the results are expressed as cc./min. Thyroidal clearances were calculated from the percentage of the dose taken up by the thyroid during an interval, divided by the percentage of the dose per liter of serum at the mid-point of the interval and by the time of the interval in minutes; the results are also expressed as cc./min.

IV. *The stable iodine uptake and thyroid hormone utilization*

The amounts of iodine released by the peripheral utilization of thyroid hormone were calculated by multiplying the inorganic iodine content of the iodine space by the average per cent per hour fall in the urinary iodine specific activity. These values were compared with the rate of stable iodine uptake and the rate of stable iodine excretion (Table 2). Although the values agree only approximately, they suggest that these patients were in fair equilibrium as far as the relationship of stable iodine uptake by the thyroid gland to thyroid hormone output and peripheral utilization was concerned, and that the stable iodine uptake might be taken as an index of over-all iodine turnover.

V. *The stable iodine uptake and the serum protein-bound iodine concentration*

In 25 patients, selected because the radioiodine uptake as compared with

TABLE 2

Patient	Thyroid hormone utilization (γ/hr.)	Stable iodine uptake (γ/hr.)	Stable iodine excretion (γ/hr.)
MU	86	93	13
CS	38	22	24
CO	10	4	10
SU	10	5	6

Thyroid hormone utilization was calculated by multiplying the iodine content of the iodine space (serum inorganic iodine concentration in micrograms per 100 cc. multiplied by the iodine space in liters) by the average per cent per hour fall in urinary specific activity; the result is expressed as micrograms per hour.

the serum protein-bound iodine concentration was above the average value, the twenty-four-hour uptake of stable iodine was plotted against the serum protein-bound iodine concentration (Fig. 4). There was a good correlation between the two values ($r = .82$, p less than .01). On a semilogarithmic plot, a line fitted to the values obtained seemed to show a relationship which would indicate that an increase of 3.5 micrograms per 100 cc. in the serum protein-bound iodine concentration was associated with a threefold increase in the stable iodine uptake. It is interesting that this relationship seemed to hold in the low and normal as well as in the hyperthyroid ranges.

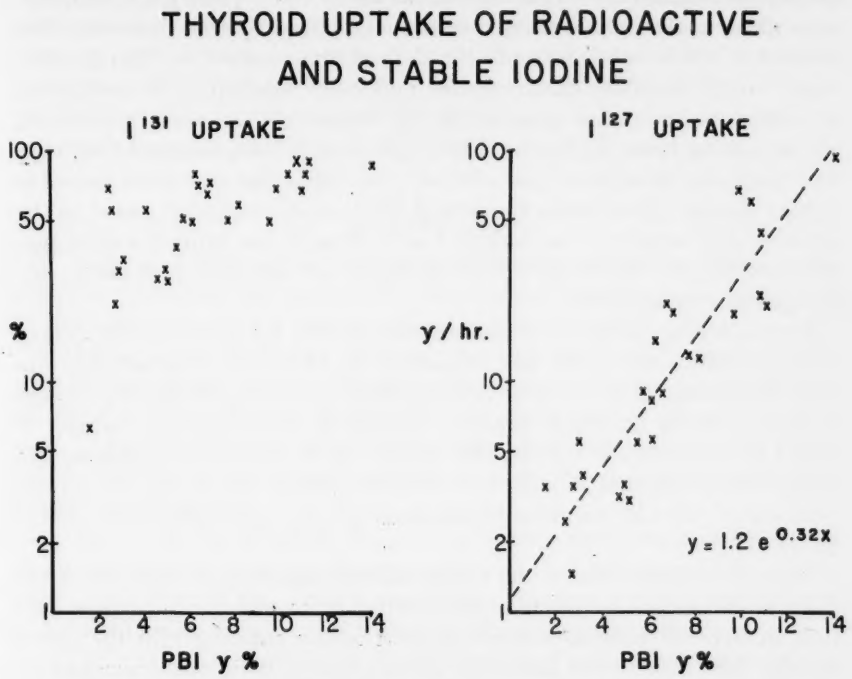

FIG. 4. The thyroidal uptake of stable iodine (I^{127}) is plotted against the serum protein-bound iodine concentration in micrograms per 100 cc. The semi-logarithmic plot enables a straight line to be fitted to the points of stable iodine uptake with the slope $y = 1.2e^{0.32x}$.

DISCUSSION

Any attempt to correlate the stable iodine uptake by the thyroid gland with thyroid hormone output and peripheral utilization must take into account the iodine storage capacity of the intact thyroid gland. It has been shown that a threefold increase in the serum inorganic iodine concentration does not appreciably depress the rate of radioiodine uptake by the thyroid

gland (5). However, average values from random samples of patients should be applicable to a hypothetical individual in iodine balance with the environment, in whom the thyroidal uptake of stable iodine is equal to thyroid hormone iodine output and peripheral utilization.

In such a hypothetical "average" individual, 40 per cent of a tracer dose of radioiodine might be taken up by the thyroid gland and the remaining 60 per cent excreted in the urine (except for a negligible percentage of the dose which would appear in the serum as thyroid hormone radioiodine, and sweat and feces radioiodine). The 60 per cent in the urine could represent dietary iodine, and the 40 per cent taken up by the thyroid gland could be equivalent to the iodine released from metabolized thyroid hormone. The amount of stable iodine going to the thyroid gland would, in this example, equal two thirds of the dietary iodine and would also equal the amount of thyroid hormone iodine released in the tissues. If the same amount of iodine is being taken up by the thyroid gland as is being released from thyroid hormone breakdown per unit of time, then the rate of radioiodine uptake should approximate the rate at which stable iodine is added to the extracellular iodine pool as reflected by a drop in the urinary iodine specific activity. In the 4 individuals in whom we obtained such data, this relationship seems likely.

Estimation of the stable iodine uptake corrects for variations in dietary iodine to which the gland has responded by changing its percentage uptake, but would be of no value in a situation in which a temporary change in dietary iodine occurred without a change in the radioiodine uptake. It would be of particular value under conditions in which the appearance of goiter were dependent on a chronic iodine deficiency, for giving not only an estimate of thyroid hormone production but also an explanation for the goiter (7).

It would appear that in the euthyroid individual up to one-half of the daily stable iodine turnover is contributed from endogenous stores, and that in hyperthyroidism the endogenous iodine entering into the extracellular fluid may be ten times the dietary iodine. This would account for the relative constancy of radioiodine uptakes in a given individual, even when deprived of dietary iodine for a considerable interval (6). The amount of iodine released as hormonal iodine following radioiodine therapy for hyperthyroidism may account for the transient depression of the radioiodine uptake which has been reported immediately following such therapy (8).

Assuming that we have examined a random sample of patients in a coastal area, it is of interest that our values for normal stable iodine uptake are in agreement with others reported from this area (6), although somewhat higher than those reported from an iodine-deficient region (7). The normal range for daily hormonal iodine output, from our data, would be

84 to 240 micrograms—the equivalent of 130 to 390 micrograms of thyroxine. This is in the range of the oral synthetic thyroxine dosage required to restore myxedematous patients to a euthyroid state, and to suppress the radioiodine uptake more than 50 per cent in euthyroid subjects (9).

The threefold increase in stable iodine uptake occurring with an increase of 3.5 gamma per 100 cc. in the serum protein-bound iodine concentration is in conformity with the increase in thyroxine utilization which has been reported in hyperthyroidism by others (10) (11) and also with the reported increase in thyroid hormone utilization in hyperthyroid patients (12).

Following therapy for hyperthyroidism, the iodine storage capacity of the thyroid gland may be reduced and the radioiodine uptake may become more responsive to variations in dietary iodine intake or in the peripheral utilization of thyroid hormone than is apparently the case in the intact gland. This may account in part for the greater individual variations in radioiodine uptake at different levels of serum protein-bound iodine observed in the treated patients.

CONCLUSIONS

1. The radioiodine uptake by the thyroid shows a significant correlation with the serum protein-bound iodine concentration in normal subjects and in patients with thyroid disease who have not received therapy.
2. In patients who have received therapy for hyperthyroidism, the radioiodine uptake values corresponding to each serum protein-bound iodine level show greater variation than in the untreated group.
3. The stable iodine uptakes in a small group of patients with high radioiodine uptakes show a good correlation with the serum protein-bound iodine concentrations.
4. The stable iodine uptake apparently bears a direct relationship to the serum protein-bound iodine concentration, so that increases of 3.5 micrograms per 100 cc. in the serum protein-bound iodine concentration indicate a threefold increase in thyroid hormone output and utilization.
5. Estimations of thyroid hormone output and utilization, derived from the average figures for stable iodine uptakes, agree well with those of other published studies.

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THE BLOOD LEVEL AS A GUIDE TO THERAPY WITH RADIOIODINE*†

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REPORTS from many medical centers have shown the unusual efficacy of radioiodine in the treatment of hyperthyroidism. Two problems still incompletely evaluated are the possible complications from such intense radiation and the dosage of radioiodine necessary to produce the desired effect. Only the problem of dosimetry will be discussed here.

The increasing use of radioiodine in the treatment of younger patients makes it even more desirable to produce a remission with the minimal amount of radiation. Since patients vary markedly with regard to the size of the thyroid and the rate at which the thyroid pool of iodine is turned over, it is necessary to individualize the dose for each patient. A preliminary tracer study should reveal the turnover time in the thyroid, so that the integrated amount of a subsequent therapeutic dose which will remain in the thyroid can be calculated. Unfortunately this requires observations *in vivo* for many days (usually at least twenty), thus making the data difficult to obtain under ordinary conditions.

From observations of only three or four days' duration, calculation of a half-life for radioiodine in the thyroid is frequently quite inaccurate, particularly when the half-life is long (thirty or forty days) or when it is a complex of several exponential rates. Such tracer studies furthermore suppose that a therapeutic amount of radioiodine is handled in exactly the same manner as the tracer dose. Miller has noted that frequently the

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rates of disappearance from the thyroid of a therapeutic and of a tracer dose of radioiodine differ markedly (1). This is hardly surprising, as the therapeutic dose by definition is presumed to alter the physiologic function of the thyroid. The radioiodine lost from the thyroid represents labeled thyroid hormone secreted into the blood stream. Therefore the amount of radioiodine in the blood after the iodide phase is completed is a function of the rate of loss of I^{131} from the thyroid. This suggests that even a single estimation of the amount of labeled thyroid hormone in the blood may be used advantageously to estimate the turnover rate of iodine by the thyroid. In forty-eight hours the uptake of the tracer dose can be measured, the amount of radioiodine in the blood determined, the thyroid weight estimated, and a therapeutic dose calculated. The present study is an investigation of the practicability of such a procedure.

METHODS

The 116 patients with hyperthyroidism included in this study were treated at Memorial Hospital between 1949 and 1952. All patients had unequivocal hyperthyroidism from a clinical standpoint, confirmed by the usual laboratory procedures including determination of serum protein-bound iodine concentration.

Patients who were not completely studied for at least nine months after treatment with radioiodine were not included. Patients with substernal thyroids or with renal disease were excluded from the group in whom blood iodine levels were determined and thyroid weights estimated.

All patients received test doses of I^{131} (10 to 300 microcuries, with less than 10 micrograms of carrier iodide). The urinary excretion was measured daily for two days and the thyroidal uptake was determined at forty-eight hours. Similar measurements were made after administration of the therapeutic dose. The concentration of I^{131} in whole blood forty-eight hours after the tracer and forty-eight hours after the therapeutic dose, was measured in 72 patients. Patients were followed for from nine months to three years after treatment and their status was determined by the usual clinical and laboratory findings. All radioiodine was received from Oak Ridge and standardized at the Sloan-Kettering Institute. The concentration of radioactivity in blood, urine and the thyroid was determined by methods discussed previously (2). The accepted value for thyroid weight was the average of three observers' estimations.

RESULTS

The initial dose of radioiodine administered therapeutically ranged from 3.85 millicuries to 26.8 millicuries, and the mean dose was 10.7 millicuries. The mean dose concentrated in the thyroid was 130 microcuries per gram of estimated thyroid weight and ranged from 60 microcuries per gram to 250 microcuries per gram. Table 1 shows the final results of treatment.

TABLE 1. RESULTS OF TREATMENT WITH RADIOIODINE IN HYPERTHYROIDISM (115 PATIENTS)

Status	After first dose	After second dose
Euthyroidism	61%	76%
Hypothyroidism	23%	24%
Persistent hyperthyroidism	16%	0%

If, by means of a tracer dose, one wishes to predict the therapeutic dose that should be administered, both the tracer dose and therapeutic dose must give consistent results. Table 2 shows a comparison of the thyroidal uptake and the blood iodine levels forty-eight hours after tracer and therapeutic doses. Generally there is very little difference in the thyroidal uptake between tracer and therapeutic doses if the time interval between the two doses is short. The blood levels show a rather surprising and consistent difference between tracer and therapeutic doses. Since it is a reasonably consistent deviation it does not necessarily invalidate the usefulness of the blood level in planning a therapeutic dose.

TABLE 2. COMPARISON OF THYROIDAL UPTAKE AND BLOOD LEVEL OF I^{131} AFTER TRACER AND THERAPEUTIC DOSES

	I^{131} (tracer/therap.)* ratio	No. of cases*	I^{131} (tracer/therap.)† ratio	No. of cases‡
Thyroid uptake	1.03 ± 0.12	27	1.13 ± 0.33	31
Blood level	1.45‡	15	—	—

* Tracer and therapeutic doses given within two weeks.

† Tracer and therapeutic doses separated by interval greater than two weeks.

‡ Correlation coefficient is 0.68.

There are several possibilities to account for the discrepancy between blood iodine levels after a tracer and after a therapeutic dose. Labeled thyroglobulin may have been released as a result of the intense radiation from the therapeutic I^{131} (3). The radiation is not as intense, however, as the minimum amount that we have previously calculated to be necessary in order to produce this effect. Furthermore, the release of thyroglobulin does not usually occur for at least three or four days after the administration of I^{131}. Release of thyroglobulin, of course, would lower the tracer-therapeutic ratio and not raise it. The correlation coefficient of 0.68 indicates that there is a fairly consistent relationship between the tracer and therapeutic blood levels. It has been suggested that, within limits, the

concentration of radioiodine in the thyroid is not correlated with its therapeutic effect. This was investigated. Figure 1 shows the proportion of patients treated who were made hypothyroid, or in whom the dose proved inadequate, compared with the concentration of radioiodine in the thyroid forty-eight hours after its administration. It is not surprising to find that a cause (radiation) and effect (reduction in thyroidal activity) relationship is apparent. Using only this parameter of dosage, it appears that at the level of 125 microcuries per gram the majority (about 60 per cent) of the patients are rendered euthyroid; among the remainder, about equal numbers of patients either require additional treatment or become hypothyroid.

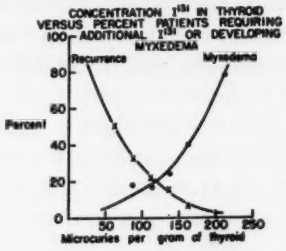

FIG. 1. Concentration of a therapeutic dose of I^{131} in the thyroid glands of hyperthyroid patients versus the percentage of such patients in whom additional treatment was required, or in whom myxedema developed.

The amount of radioiodine in the blood two or more days after a tracer or after a therapeutic dose is well known to be elevated above the normal range in patients with hyperthyroidism (4). The great range of values for the blood iodine level seen in patients with hyperthyroidism is not, perhaps, generally appreciated. Table 3 shows these values in various groups of hyperthyroid patients. It is apparent that previous treatment has a definite effect on the blood level. Previous thyroidectomy seems to result in an increase in the blood level, whereas treatment with iodine results in a decrease. The remnant of gland remaining after thyroidectomy cannot contain a very large amount of iodine, and to secrete thyroid hormone at an increased rate its turnover time must be abnormally rapid, resulting in a high blood iodine level. It is also possible that patients with high blood levels are those in whom there will be a recurrence after thyroidectomy. Previous treatment with iodine, on the other hand, by increasing the amount of iodine stored in the thyroid, will cause a decrease in the thyroid iodine turnover rate and hence in the blood level. This will occur even when the thyroid continues to secrete thyroid hormone at the same absolute rate. It is somewhat surprising to find that previous treatment with antithyroid drugs does not increase this blood level by decreasing the amount of iodine stored in the thyroid.

TABLE 3

Group	Blood radioiodine level*		No. of cases
	Avg.	Range	
All patients	0.475±0.459**	0.036 to 1.69	72†
Patients previously thyroidectomized‡	0.820±0.416	0.334 to 1.61	10
Patients with no previous medication	0.507±0.343	0.151 to 0.977	12
Patients previously given antithyroid drugs§	0.448±0.400	0.101 to 1.69	27
Patients previously treated with iodine‖	0.196±0.115	0.036 to 0.467	17

* All values are in terms of percentage of dose per liter of whole blood, forty-eight hours after the dose.

** Average and standard deviation.

† Since some patients received both antithyroid drugs and iodine, the total number of cases is greater than the sum of the 4 categories listed.

‡ These patients had had no treatment since a recurrence following thyroidectomy.

§ These patients received only the antithyroid drugs, propylthiouracil and methylmercaptoimidazole. (Patients receiving 5-iodothiouracil are not included.) These drugs were discontinued at least two days prior to receiving radioiodine.

‖ These patients received only iodine, which was stopped from one to three weeks prior to the radioiodine therapy.

We were interested in learning whether there was any correlation between the level of radioiodine in the blood and the 48-hour uptake by the thyroid. In Figure 2 it may be seen that in general there is no correlation at the lower blood iodine levels, but at higher blood levels the 48-hour uptake is fairly constant at between 40 and 60 per cent of the dose.

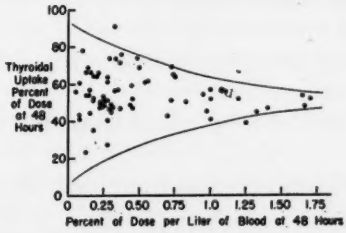

FIG. 2. Correlation of levels of I^{131} in the blood and in the thyroid of patients with hyperthyroidism forty-eight hours after a tracer dose of I^{131}.

This is understandable, since patients with very high blood levels discharge iodine at such a rapid rate from their thyroids that within forty-eight hours after the dose has been administered, much of it has already

left the thyroid. We have described this sequence of events previously (5). These patients with high blood levels undoubtedly have the most rapid turnover rates and hence receive the least radiation to the thyroid. Figure 3 shows the correlation between the blood level and the percentage of pa-

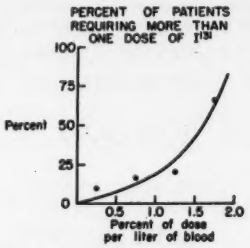

FIG. 3. Percentage of patients with hyperthyroidism grouped according to blood level, who required more than one therapeutic dose of I^{131}.

tients showing that specific blood level who require further treatment. It is apparent that inadequate treatment is usually associated with a high blood level. Figure 4 shows the average number of microcuries deposited per gram of thyroid tissue in patients who became euthyroid, in those who became hypothyroid, and in those who require additional treatment—when such patients were first grouped according to blood level. It may be seen that, on the average, the higher the blood level, the more radioiodine there must be concentrated in the thyroid forty-eight hours after a therapeutic dose, in order to produce remission in the hyperthyroidism.

If one assumes that the relationship in the euthyroid cases between blood level and microcuries deposited per gram is linear, an equation can be derived by the method of least squares giving the best fit to the experimental points. The equation so derived from the data on 43 patients who became euthyroid after a single dose of I^{131} is:

$$Y = 110 + 27\,B$$

where Y = microcuries to be deposited per gram of thyroid tissue at forty-eight hours, and

B = concentration of I^{131} in whole blood forty-eight hours after the dose.

For calculation of a therapeutic dose from tracer data, the following is the complete equation:

$$D = \frac{100\ (110 + 27\,B) \times G}{U}$$

where D = dose to be given, in microcuries,

G = weight of thyroid, in grams, and

U = percentage uptake of tracer dose in forty-eight hours.

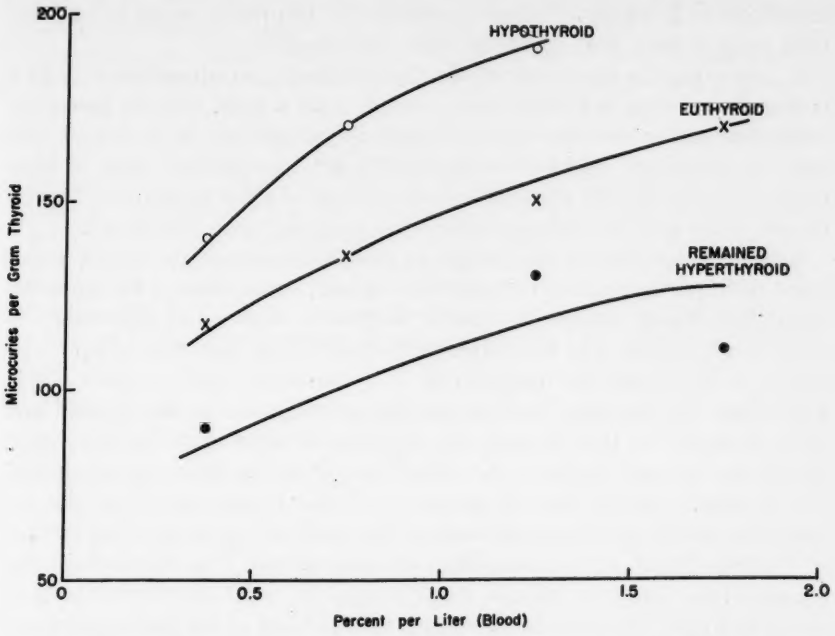

FIG. 4. Results of treatment with I^{131} in patients with hyperthyroidism first grouped according to blood level—and the average microcuries per gram of thyroid tissue calculated for each group.

DISCUSSION

There are several factors which may operate to make the calculations just presented grossly inaccurate. In the main, these are:

1. Error in estimation of thyroid weight. This is particularly evident in patients having a portion of the thyroid located in the chest. Thus, in the data of Figures 1 and 4, cases with substernal goiter were excluded. Even when allowing for omission of these cases, estimation of thyroid weight by palpation is inaccurate, although Williams has presented evidence that his predictions were almost always within ± 15 per cent of the actual weight determined when such thyroids were removed surgically (6).

2. Uneven distribution of radioiodine. Radioautographs show that at any given time the I^{131} in the thyroid is usually not evenly distributed. This results in excessive radiation in some areas and inadequate radiation in other areas. Usually this variable is ignored, as it is impossible to control or evaluate it, and we shall do likewise.

3. Renal disease will diminish the rate of excretion of iodide from the blood, so that forty-eight hours after administration of I^{131} much of the

radioactivity in whole blood will be iodide. In the present study all patients with renal disease were excluded from consideration.

4. Variations in sensitivity of the thyroid gland to radioiodine may be a factor. It has been suggested that patients with a toxic nodular goiter are more resistant to therapy with radioiodine than patients with Graves' disease (7). Although we have treated only a few unequivocal cases of toxic nodular goiter, this did not appear to be a factor of great magnitude. Nevertheless, cases of toxic nodular goiter were excluded from this study.

Any consideration of the dosage of radioiodine employed in the treatment of hyperthyroidism must include careful evaluation of the ends desired. If a young, otherwise healthy individual with a life expectancy of forty or fifty years is to be treated with radioiodine, one may compromise with the thyrotoxicosis temporarily, if by so doing one can more surely administer the smallest possible amount of radiation to the thyroid and body generally. In this instance, the objective of rapid control of the hyperthyroidism should probably be subordinated to the desire to administer the smallest possible dose of radiation. Under these conditions, the administration of multiple small doses of radioiodine is probably the method of treatment that best accomplishes the desired end. The calculations presented here, therefore, require modification, in order to reduce the incidence of hypothyroidism as much as possible. Most of the patients treated at Memorial Hospital, however, have a short life expectancy, either because of age or because of other disease (such as hypertensive cardiovascular disease or carcinoma). In these patients delivery of the minimal amount of radiation is less important than early control of the hyperthyroidism. In either situation, estimation of the level of radioiodine in the blood will permit us to adjust the dosage so that the probability of achieving the desired effect is increased.

SUMMARY

The results of treatment of 116 patients with hyperthyroidism by means of radioiodine have been compiled.

A positive correlation was found between the level of radioiodine in the blood forty-eight hours after a therapeutic dose and the incidence of inadequate dosage.

On the basis of blood iodine levels in 43 cases of hyperthyroidism rendered euthyroid with one dose of I^{131}, an equation for prescribing the dose to be administered has been derived.

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THE UPTAKE OF RADIOACTIVE IODINE BY CARCINOMA OF THE THYROID GLAND: A STUDY OF 128 CASES*†

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IT IS known that certain carcinomas of the thyroid gland are capable of concentrating radioactive iodine, and that this function may be correlated more or less with certain structural qualities of the lesion (1–6). Lesions most likely to pick up iodine are the less anaplastic carcinomas with an orderly arrangement of cells in a follicular pattern, particularly if the follicles contain colloid-like material (2). Conversely, lesions without a follicular component usually do not possess this function. There are, however, apparently so many exceptions to these generalizations that it has been proposed recently that in the case of all patients with distant metastatic lesions from carcinoma of the thyroid an effort should be made to bring them to a treatable stage with radioactive iodine (7).

It would be more desirable, obviously, to undertake such treatment only in those cases in which the lesions concentrated or could be made to concentrate sufficient radioactive iodine to affect the carcinoma. Unfortunately, the ultimate uptake of iodine can be determined with complete certainty only after ablation of the thyroid and prolonged treatment with thiouracil, an undertaking of considerable magnitude and of some risk. The present study was made in order to determine, if possible, whether or not patients with inoperable carcinoma of the thyroid could be selected for treatment with radioactive iodine with some confidence, on the basis of the type and histologic features of the lesion. In general, the findings suggest that certain lesions probably cannot be made to concentrate sufficient iodine to make treatment feasible. In the case of other lesions, the ultimate uptake can be judged only after stimulation. Finally, in a third group, the uptake of iodine is so good that treatment should be possible in all cases.

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† The radioisotopes utilized in the studies reported on in this paper were supplied by the United States Atomic Energy Commission.

It is probably unnecessary to point out that isotopic irradiation has no place in the treatment of operable lesions. Treatment, as used in this report, applies only to local extensions or distant metastases of thyroidal carcinoma which cannot be removed surgically.

MATERIALS AND METHODS

All cases of carcinoma of the thyroid gland in which radioactive iodine was used either diagnostically or for treatment at the Mayo Clinic have been reviewed. The initial thyroidal uptake, that is, uptake in the presence of the normal thyroid, was studied in 115 cases by means of autoradiograms.

The autoradiograms were prepared by the method of Hamilton (8). Mounted paraffin sections, usually 10 microns in thickness, were placed against the emulsion side of standard x-ray films for three and ten days in light-tight boxes. The films were then developed and the slides processed and stained. In most cases, the patient received 300 microcuries of I^{131}, twenty-four to forty-eight hours before operation. In the more recent cases the amount of I^{131} was increased to 500 microcuries and one set of films only was exposed for five days. In all instances there was sufficient radioactivity in normal thyroid tissue to cause dense blackening of the film. The uptake of radioactive iodine by carcinomatous tissue, as judged by the degree of darkening of the film, varied from none to an amount sufficient to cause the same degree of blackening as did normal thyroid.

Positive autoradiograms were secured under these conditions from tissue which contained less than 1 microcurie per gram of I^{131}. The tissue from which the autoradiogram shown in Figure 1*a* was made concentrated 0.2 microcurie per gram and that from which Figure 1*b* was made retained 0.5 microcurie per gram. Both autoradiograms were considered to show moderate uptake.

Relatively fewer cases were available for study after the thyroid had been ablated and the uptake of iodine had been stimulated by treatment with either thiouracil, thyrotropic hormone or both. In several of the treated cases, autoradiograms were not made originally, and in practically none was tissue available for the preparation of subsequent autoradiograms. The ultimate uptake in such lesions was judged by *in vivo* counting, by urinary excretion and, in several cases, by objective evidence that the lesion had been affected by the internal irradiation.

CLASSIFICATION OF CARCINOMA OF THE THYROID

The classification which is given has long been employed at the Mayo Clinic. In this classification, thyroid cancer is divided into three main groups:

1. Papillary adenocarcinoma.
2. Malignant adenoma.
3. Anaplastic carcinoma.

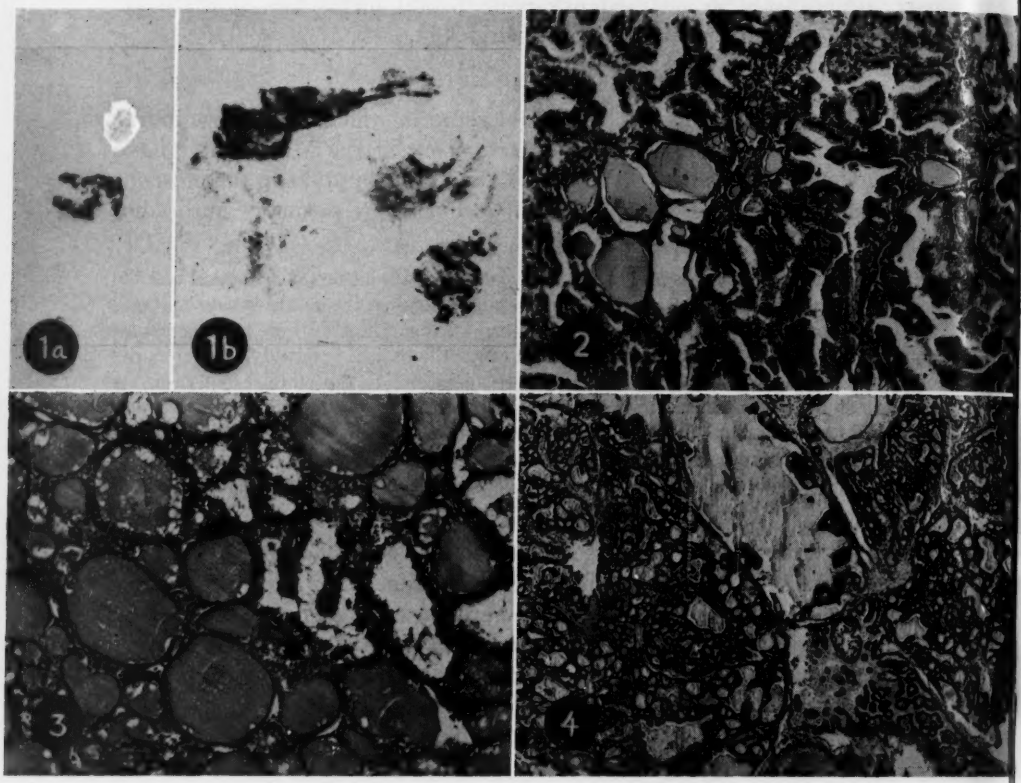

FIG. 1, *a* and *b*. Autoradiograms showing moderate concentration of radioactive iodine in 2 cases of thyroid carcinoma.

FIG. 2. Papillary adenocarcinoma of thyroid. There is slight colloid production but the tumor is predominantly papillary in structure (hem. & eos.; ×100).

FIG. 3. Papillary adenocarcinoma of thyroid, follicular type. The section is from a metastatic lesion in a lymph node. This tumor is almost entirely follicular in structure, resembling normal thyroid in areas (hem. & eos.; ×100).

FIG. 4. Papillary adenocarcinoma of thyroid, mixed papillary and follicular type. There is an intimate mixture of papillary and follicular structure (hem. & eos.; ×32).

The first two groups, in general, include the more slowly growing carcinomas. In group 3 are included the more anaplastic or undifferentiated tumors. It should be understood that the terms used to designate the first two groups are generic and not descriptive. We agree with Graham (9) that the two types of lesions differ sufficiently in their biologic behavior to warrant their being considered as essentially different types of lesions.

In group 1 are placed all tumors of papillary type, including those with a mixture of papillary structure and colloid-containing follicles. The latter may be so abundant as to make up the bulk of the tumor. No apparent difference in rate of growth or metastasizing tendency has been noted within this group, regardless of the proportion of papillary or follicular structure in the tumor.

Since function is grossly correlated with the presence of follicles and particularly with follicles containing colloid, we have, for the purposes of this study, subdivided the papillary group into subgroups based on the proportion of follicles and colloid in the tumor. A lesion was considered predominantly papillary if follicle formation occurred in less than 10 to 15 per cent of the tumor. A typical example of this subgroup is shown in Figure 2. At the other extreme, if 80 to 90 per cent or more of the tumor showed follicles, usually with colloid, the lesion was classified as predominantly follicular, as shown in Figure 3. It is to be noted that follicular carcinomas of this type may rather closely approximate normal thyroid in appearance. Between the two extremes there is a large group of papillary carcinomas designated mixed papillary and follicular type. In these the proportion and relationship of papillary structure and follicle formation vary from case to case. Sometimes there is an intimate mixture throughout the tumor as shown in Figure 4; sometimes there is a spotty distribution in which completely papillary areas occur in one part of the tumor, and completely follicular areas elsewhere (Fig. 5). Occasionally the primary tumor and metastatic nodes may be unlike in structure, one being predominantly papillary, the other follicular in type (Fig. 6). There were few instances of this type of distribution in our study, and they are classified as mixed follicular and papillary.

In group 2 are included all thyroid carcinomas (excluding papillary tumors) occurring in circumscribed nodular form surrounded by a fibrous capsule. A microscopic section through such a carcinoma is shown in Figure 7. In the more benign-appearing tumors of this group, as has long been noted, the resemblance to fetal adenoma may be striking; hence the term "malignant adenoma." Venous invasion with consequent metastasis through the blood stream is a common method of spread. Regional nodal metastasis is less common than in the papillary group. The term "malignant adenoma" is admittedly a poor one. As used in this study it does not imply that the tumor necessarily arose in a pre-existing benign adenoma.

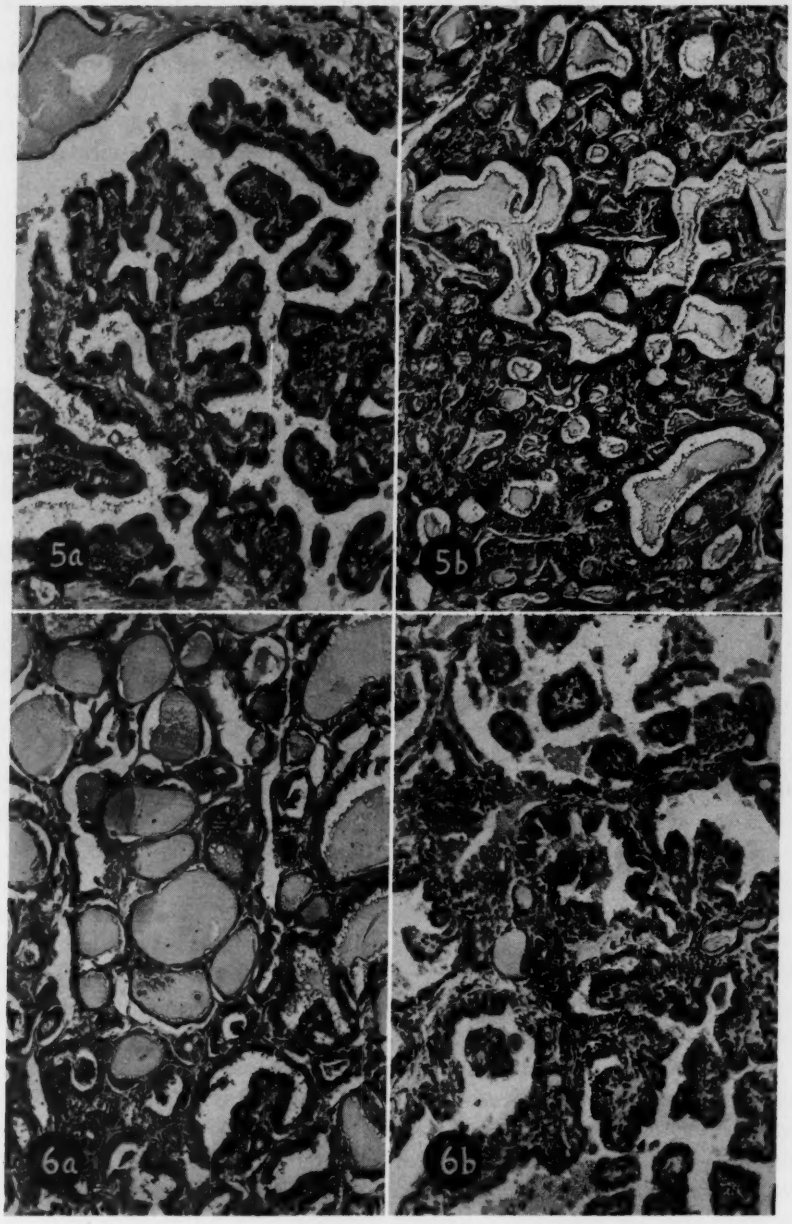

FIG. 5. Papillary adenocarcinoma of thyroid, mixed type. *a*. Completely papillary area (hem. & eos.; ×110). *b*. Follicular area in the same tumor (hem. & eos.; ×110).

FIG. 6. Papillary adenocarcinoma of thyroid, mixed type. *a*. Primary tumor in thyroid, predominantly follicular (hem. & eos.; ×110). *b*. Metastasis to lymph node from this tumor, predominantly papillary in structure (hem. & eos.; ×110).

A variety of histologic patterns is seen in this group. The most benign-appearing tumors contain small follicles closely resembling fetal adenoma. Most tumors of this group, however, in addition to small follicles, contain areas in which the cells are arranged in sheets without any demonstrable pattern. Depending on the proportion of these two components, these lesions were classified as predominantly solid if follicles were absent or only occasionally present (Fig. 8). If more than 80 per cent of the tumor was follicular, the lesion was classified as follicular type (Fig. 9). Finally, many lesions fell between these two extremes (Fig. 10).

Hürthle-cell carcinomas usually occur in nodular circumscribed form and are included with the malignant adenoma group. These tumors are characterized by large cells with voluminous acidophilic cytoplasm. Follicle formation is usually absent (Fig. 11). The majority of these tumors are of a low or moderate degree of malignancy.

All other thyroid carcinomas are included under the heading of anaplastic carcinoma. This group includes spindle-cell and giant-cell carcinoma, small-cell anaplastic carcinoma, clear-cell carcinoma, and other variants of anaplastic thyroid cancer.

The classification and number of cases studied are shown in Table 1.

RESULTS

Papillary adenocarcinoma.—In 24 cases the lesion was considered to be of the predominantly papillary type. The initial uptake of radioactive iodine was nil in all cases. An attempt was made to stimulate uptake in 1 case (Fig. 12), in which the lesion was locally inoperable and resection of the normal thyroid tissue was technically impossible. Myxedema devel-

TABLE 1. CASES OF CARCINOMA OF THE THYROID GLAND IN WHICH RADIOACTIVE IODINE WAS USED EITHER DIAGNOSTICALLY OR FOR TREATMENT

	No. of cases	
I. Papillary adenocarcinoma		70
Predominantly papillary	24	
Mixed papillary and follicular	32	
Predominantly follicular	14	
II. Malignant adenoma		25
Predominantly solid	10	
Mixed follicular and solid	6	
Predominantly follicular	3	
Hürthle-cell carcinoma	6	
III. Anaplastic carcinoma		33
Total		*128*

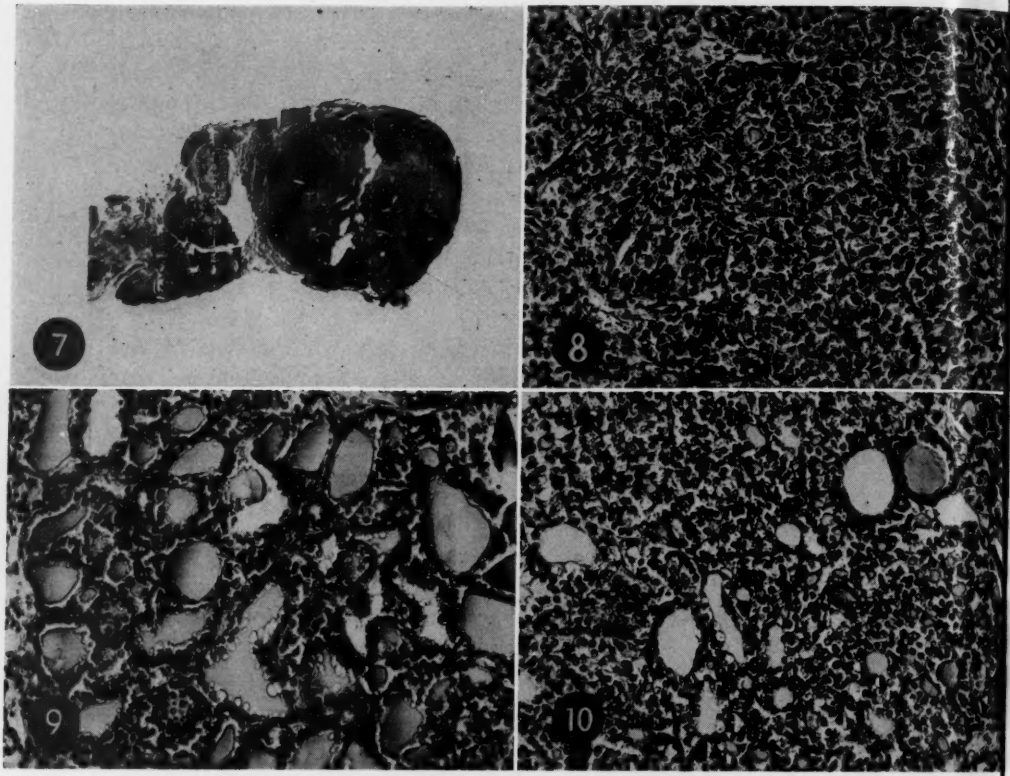

FIG. 7. Malignant adenoma of thyroid. The carcinoma is well circumscribed and there is a thick fibrou capsule (actual size). There was metastasis to the femur in this case.

FIG. 8. Malignant adenoma of thyroid. Solid carcinoma in which the cells are arranged in sheets wit little or no follicle formation (hem. & eos.; ×140).

FIG. 9. Malignant adenoma of thyroid. This tumor shows a follicular structure (hem. & eos.; ×140).

FIG. 10. Malignant adenoma of thyroid. Histologic section to show mixed follicular and solid carcinom (hem. & eos.; ×140).

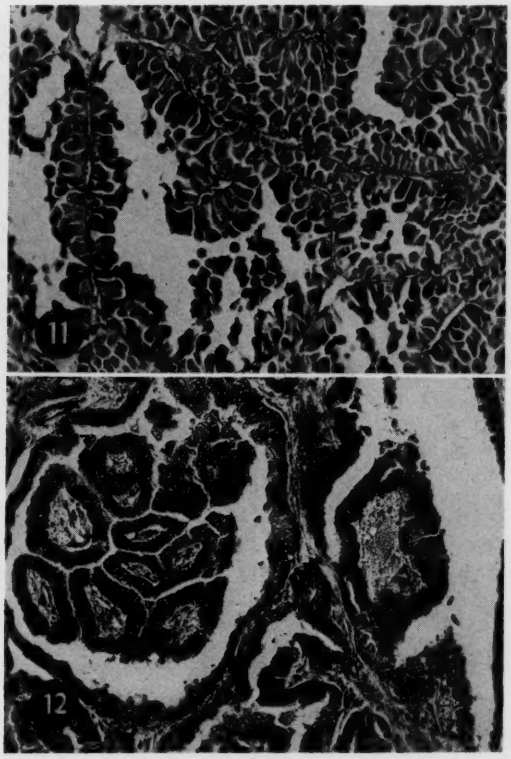

FIG. 11. Hürthle-cell carcinoma. Note the large cells, voluminous cytoplasm and absence of colloid. This tumor had invaded the jugular vein (hem. & eos.; ×135).

FIG. 12. Papillary adenocarcinoma of thyroid. There is virtually no follicle formation or colloid production in this tumor (hem. & eos.; ×95).

oped after ablation of the thyroid by means of radioactive iodine. The patient received 1 gram of thiouracil per day for six months. No uptake of radioactive iodine was demonstrable before or after treatment, either by counting *in vivo* or by the counting of digests of resected tissue.

Thirty-two cases of mixed papillary and follicular adenocarcinoma were studied. The initial uptake was determined in 28. There was no uptake in 14 cases, slight uptake in 9, moderate uptake in 4 and marked uptake in 1. Lesions in which follicles were small or those in which there was little colloid formation, as a rule, did not concentrate iodine. Similarly, if follicular formation was spotty, even if the follicles were of good size and contained normal-appearing colloid as shown in Figure 5, the uptake was usually nil. Failure to concentrate iodine initially was not, however, limited to lesions with such histologic features. In several cases in which no uptake was demonstrable the lesions were indistinguishable from others in which the up-

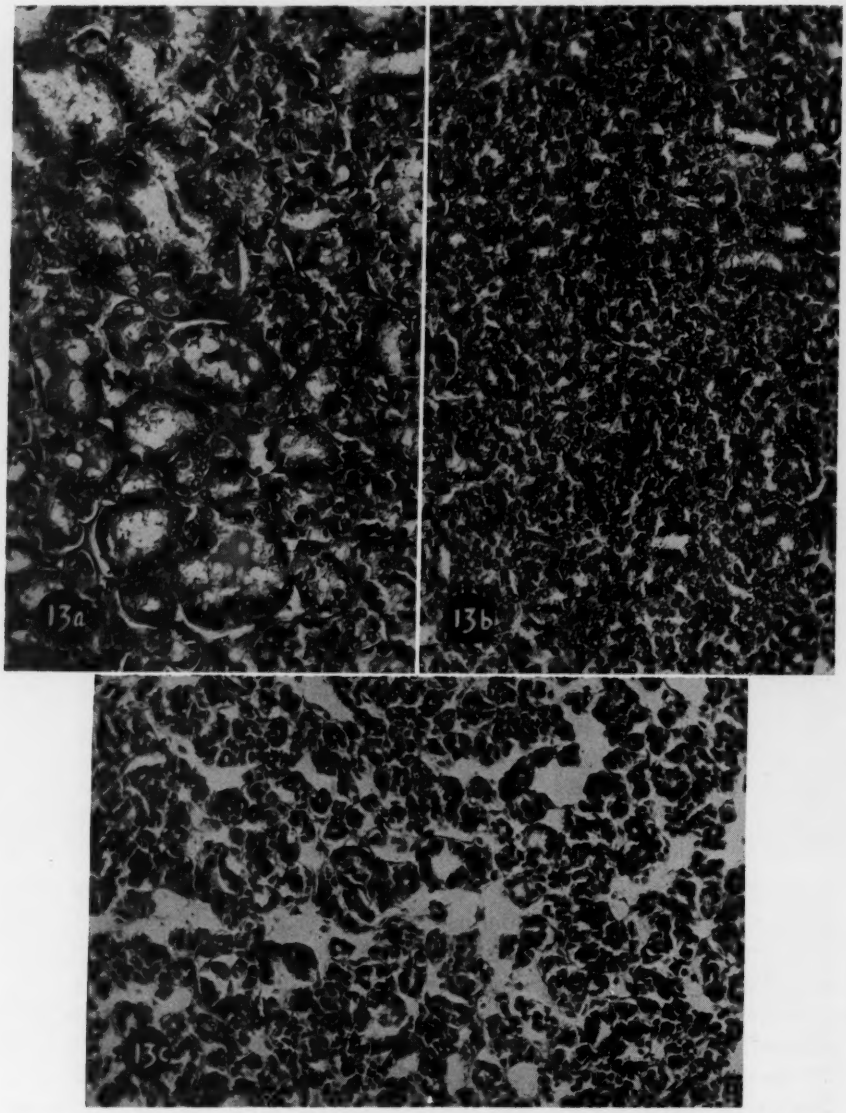

FIG. 13. Malignant adenoma of thyroid. *a*. Area of follicular carcinoma (hem. & eos.; ×175). *b*. Area of less marked follicle formation and solid carcinoma (hem. & eos.; ×175). *c*. Histologic structure of osseous metastatic lesion in this case. Note small follicles with little or no colloid (hem. & eos.; ×175).

take was moderate. In the 1 case in the group in which the uptake was marked the follicles were so large that they could be more accurately described as cysts. The cysts were distended with colloid, which was vacuolated peripherally.

Treatment was attempted in 5 cases of the mixed type. In 3 cases treatment was successful to the extent that the lesions became smaller. In the fourth case the thyroid was ablated by 50,000 microcuries of radioactive iodine. The patient was treated subsequently with thiouracil for six months. No uptake ever was demonstrable in a pulmonary metastatic lesion. The

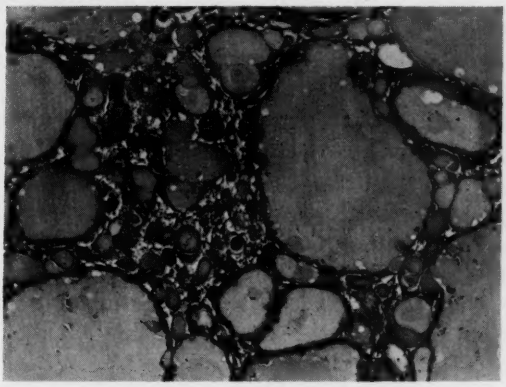

FIG. 14. Malignant adenoma of thyroid. Histologic section of metastatic nodule. Note the resemblance to benign microfollicular and macrofollicular adenoma (hem. & eos.; ×95).

initial uptake in the primary tumor was nil. The lesion shown in Figure 4 was at least 50 per cent follicular and the majority of follicles contained colloid. Follicular regions, however, were distributed in a spotty fashion throughout the tumor, a finding usually associated, as previously mentioned, with a poor or absent uptake. In the remaining case an initial autoradiogram was not made. Myxedema developed after 50,000 microcuries of radioactive iodine had been given. No uptake could be demonstrated in a pulmonary metastasis after twenty weeks of thiouracil therapy.

In all 14 cases of the follicular type of papillary adenocarcinoma the initial uptake was at least moderate, and in most cases marked. Treatment was successful to the extent that lesions were affected in the 4 cases of this type in which it was attempted.

Malignant adenoma.—Of the 25 cases of this type studied, 10 were classified as predominantly solid. There was no initial uptake in any of the 10 cases. An attempt was made to stimulate uptake in 3 such cases. In each instance the thyroid was ablated with radioactive iodine. In 1 case myxedema developed but the patient received no antithyroid drugs; the other

2 patients received antithyroid drugs for two and four months, respectively. No uptake ever could be demonstrated in any of the 3 cases.

In 6 cases the lesions were of the mixed type. In 4 the initial uptake was moderate or marked, whereas in 2 there was no uptake initially. Treatment was successful in the 2 cases in which it was attempted. In 1 of the 2 cases in which treatment was given there was no initial uptake in either the primary lesion or an osseous metastatic lesion (Fig. 13). There was a marked uptake as determined by *in vivo* counting in the osseous metastatic lesion twelve days after total thyroidectomy.

The lesions in 3 cases were classified as follicular malignant adenomas. The initial uptake in 2, as judged by *in vivo* counting, was excellent; an autoradiogram in the third case showed no uptake. The follicles in this instance were small and virtually without colloid; the lesion was resectable so that treatment with radioactive iodine was not indicated. The 2 remaining patients were treated successfully, in that lesions diminished in size or disappeared. A metastatic lesion in 1 of the 2 cases is shown in Figure 14.

Hürthle-cell adenocarcinoma: anaplastic adenocarcinoma.—No uptake was initially demonstrable in the 6 cases of Hürthle-cell adenocarcinoma or in the 33 cases of anaplastic adenocarcinoma studied. Some attempt was made to induce uptake in 1 of the cases of Hürthle-cell carcinoma and in 8 cases of anaplastic adenocarcinoma. In all the attempt failed, in that no uptake ever could be demonstrated by any lesion.

COMMENT

Uptake of iodine in the presence of the thyroid.—The correlation between histologic structure and the uptake of iodine in the presence of the thyroid gland was such that all lesions could be assigned to one of three categories with complete confidence, on the basis of histologic structure alone. In the first category were those lesions, none of which concentrated iodine initially. Anaplastic carcinomas, the predominantly papillary type of papillary adenocarcinomas, and the Hürthle-cell and solid types of malignant adenomas made up the group. The second category included the lesions in which the uptake of iodine was invariably good. In the present study the only lesions of this type were the follicular variant of the papillary adenocarcinomas. In the case of lesions in the third group the initial uptake of iodine could not be correlated with the histologic structure of the lesions. It was necessary to assign the mixed papillary and follicular type of papillary adenocarcinoma and both the mixed follicular and solid type and the follicular type of malignant adenoma to this group.

The iodine-concentrating function of thyroidal carcinoma after stimulation.—Seidlin and his colleagues (10) and Rawson's group (11) have demonstrated that the uptake of iodine in some cases of thyroidal carcinoma can

be stimulated by ablation of normal thyroid tissue. Rawson's group has shown also that the function of concentrating iodine can be further stimulated by prolonged treatment with thiouracil (7, 12). The comparatively little information concerning uptake by various types of carcinoma after stimulation suggests that one change only can be introduced with complete confidence in the three categories of lesions described previously. Follicular and mixed follicular and solid types of malignant adenoma apparently can be stimulated to concentrate iodine in practically all instances, regardless of whether there was initial uptake or not.

Conclusions at the present time must be more guarded concerning uptake after stimulation in the case of predominantly papillary lesions and the Hürthle-cell and solid types of malignant adenomas. From the standpoint of possible treatment with radioactive iodine these lesions are of particular interest, since they progress so slowly that sufficient time is available to attempt to stimulate uptake. However, the initial uptake in the majority of reported cases of these types, as in the present study, has been minimal or nil (2, 11–13) and attempts to stimulate uptake have not been particularly rewarding (11, 12). A few cases have been reported, conversely, in which some initial uptake was found or in which uptake could be initiated or increased (1, 12). It might be well to point out that failure to stimulate uptake may be attributable to irradiation or to inadequately prolonged treatment with thiouracil (7). Consequently, one cannot conclude that stimulation of uptake is not possible in cases in which the attempt was apparently unsuccessful. Attempts to stimulate uptake will have to be made in more cases before the ultimate functional capacity of lesions of these types can be judged with certainty. It is probable, however, in the light of present evidence, that patients with such lesions should be regarded as most unfavorable candidates for treatment with radioactive iodine.

In the case of lesions of the mixed papillary and follicular type, neither the initial uptake nor the uptake after stimulation can be predicted with confidence from the histologic structure of the lesion. There is, however, a sufficient possibility that lesions of this type can be made to concentrate iodine, so that an attempt to stimulate uptake should be made in all such cases in which the lesion cannot be resected.

CONCLUSIONS

With respect to the function of concentrating iodine, carcinomas of the thyroid may be assigned to one of three categories on the basis of type and histologic structure. Lesions in one category practically invariably concentrate, or can be stimulated to concentrate iodine. The lesions in this group are the follicular type of papillary adenocarcinomas and both the follicular type and mixed follicular and solid type of malignant adenomas.

Lesions in the next category may or may not concentrate iodine initially. After stimulation, similarly, uptake may or may not be induced or increased. On the whole, the likelihood of increasing uptake is good. The only type of lesion in this category is the mixed follicular and papillary type of adenocarcinoma.

All other carcinomas of the thyroid may be placed in a third group. Uptake in the presence of the thyroid is usually nil and the likelihood of stimulating uptake is poor. Lesions in the group include the predominantly papillary type of papillary adenocarcinoma, solid and Hürthle-cell types of malignant adenoma and all anaplastic adenocarcinomas.

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TREATMENT OF THYROID CANCER METASTASES WITH TSH AND I^{131} DURING THYROID HORMONE MEDICATION*

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INTRODUCTION

THIS report consists of a review of 50 cases of cancer of the thyroid observed during the last five years. In 13 of these, euthyroidism has been maintained by medication with desiccated thyroid or sodium-*l*-thyroxine (Baxter). An increased retention of radioactive iodine under the influence of TSH was obtained in 4 of these 13 cases. The demonstration that the pituitary hormone could induce increased uptake of radioactive iodine during thyroxine medication has been made in normal medical students (unpublished data). Exogenous thyroid hormone medication depresses endogenous thyrotropic secretion. The usual management of thyroid cancer is to anticipate the beneficial effect of profound hypothyroidism in such patients (1). This effect is an increased TSH production by the pituitary, causing a chronic stimulation of the tumor and/or metastases that will result in an increased uptake of the isotope. If such an improved uptake could be induced by parenteral TSH during the pituitary suppression accomplished by thyroid hormone medication, the same therapeutic advantage would be gained with the desired reduction in rate of growth of the tumor over long periods of time. Thus the hypothesis is suggested that, by suppression of the endogenous TSH, there will be a tendency to retard the growth of the malignancy and the occurrence of metastases.

PATHOLOGIC CHARACTERISTICS

Histologically the cases were classified into general groups, using the predominant histologic pattern as the deciding factor for classification. The

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groups were: 1) papillary, 2) alveolar and follicular, and 3) a general group simply called "others." This latter group included spindle-cell, small-cell, Hürthle-cell, giant-cell, anaplastic and unclassifiable tumors.

The 50 cases were divided as follows:

Papillary	Alveolar and follicular	Others
27 cases—54%	12 cases—24%	11 cases—22%
Males—8	Males—2	Males—0
Females—19	Females—10	Females—11

The youngest patient was 5 years old and the oldest, 78. Between the ages of 21 and 30, there were 9 cases; between the ages of 31 and 40, 11 cases; and between the ages of 61 and 70, 10 cases. Four patients in this group were over 71 years of age (Table 1). Between the ages of 11 and 40 there were 34 cases, *i.e.*, nearly half the cases occurred in young people.

TABLE 1. AGE DISTRIBUTION AND RATIO OF MALES AND FEMALES

Age (yrs.)	Females	Males	Total
1–10	1 (5 yr.)	0	1
11–20	3	1	4
21–30	6	3	9
31–40	10	1	11
41–50	2	1	3
51–60	7	1	8
61–70	6	4	10
71–80	4	0	4
Total	*39*	*11*	*50*

In 6 patients the metastatic lesion was the first sign of cancer to be discovered (Table 2). There were four metastases to the cervical lymph nodes, one to the skull, and one to the manubrium. In 5 of these cases, no enlargement of the thyroid was palpable but following total lobectomy or thyroidectomy, a malignant lesion was found in the thyroid gland. In 1 case the malignant lesion was 5 millimeters in diameter. In another case, a needle biopsy of a mass in the manubrium was performed and follicular metastatic carcinoma of thyroid origin was found. An x-ray examination of the chest had shown a large mediastinal tumor, and no thyroid tissue had been palpated in the neck. At autopsy the mediastinal mass proved to be an enlarged lobe of the thyroid in which follicular and anaplastic adenocarcinoma was found.

TABLE 2. METASTASIS AS FIRST SIGN OF CARCINOMA OF THE THYROID

Patient	Age (yrs.)	Anatomic site
D.S.	*32**	Lymph node, left neck.
	33†	Thyroid not enlarged; 5-mm. lesion in upper pole left lobe
M.L.	*5*	Lymph node, right neck.
	6	Carcinoma in both lobes.
R.L.	*38*	Lymph node, neck;
	38	4-mm. lesion upper pole of right lobe.
A.W.	*67*	Sternal mass, thought to be aneurysm.
	68	Large substernal goiter, malignant.
L.S.	*27*	Lymph node, neck.
	28	Thyroid carcinoma.
E.E.	*75*	Mass, left frontal parietal area.
	75	Total thyroidectomy; lesion about 1.5 cm. left lobe.

* Age at time of microscopic diagnosis.
† Age when first seen by us.

The interval in these cases between the time of recognition of a goiter or a mass and the time of surgery and pathologic diagnosis varied from seven months to forty-one years. The survival time following surgery was from seven months to twenty-five years. Several patients are still living ten to fifteen years postoperatively—some with the disease and others with no demonstrable metastasis.

The metastases in 33 patients followed the well known pattern, that is the papillary type of malignancy travelled to the regional lymph nodes and later to the lungs, whereas the follicular type spread to the bones and lungs; metastases from the types called "others" were found in unpredictable locations (Table 3).

Metastasis to the thyroid gland is not frequent. One case, not included in this series, showed a metastatic thyroid carcinoma from a primary tumor of the rectum, classified as mucinous adenocarcinoma—Grade 4.

The association of hyperthyroidism and malignancy is a debatable question, but there was 1 case in this series. The patient was a 21-year-old woman who complained of nervousness, palpitation, profuse sweats, exophthalmos, fatigue and marked quadriceps weakness of eight months' duration. There was bilateral enlargement of the thyroid gland, the basal

TABLE 3. LOCATION OF METASTASES IN RELATION TO TYPE OF CARCINOMA

Type of carcinoma	No. of cases	Location of the metastasis
Papillary (19 cases)	15	Regional lymph node
	3	Regional lymph nodes and lungs
	1	Regional lymph nodes and axillary nodes
Follicular (7 cases)	4	Bones
	2	Bones and lungs
	1	Bones, abdominal lymph nodes, adrenals, lungs and pleura
Other (7 cases)	1	Small-cell, to regional lymph nodes
	2	Spindle-cell, to regional lymph nodes
	2	Hürthle-cell, to regional lymph nodes
	1	Anaplastic, to lungs
	1	Unclassifiable, to lungs

metabolic rate was +64 per cent, and the serum protein-bound iodine level was 14.7 micrograms per 100 cc. Propylthiouracil produced marked improvement in all symptoms and laboratory findings. At end of two months, a subtotal thyroidectomy was performed. The pathologic diagnosis was hyperplasia plus a papillary and alveolar type of carcinoma.

The number of patients still living (treated and untreated) in each group is shown in Table 4. In the first two groups (the more numerous common types of cancer) two-thirds of the patients are alive.

TABLE 4. MORTALITY IN RELATION TO TYPE OF CARCINOMA (TREATED AND UNTREATED)

Type of carcinoma	No. of cases	Deaths	Per cent
Papillary	27	10	37
Alveolar-follicular	12	4	33.3
Spindle-cell	2	1	50
Solid type	1	1	100
Giant-cell	2	1	50
Unclassified	1	1	100

An instructive study of the life cycle of carcinoma of the thyroid has been made by the senior author (C.T.S.) (Table 5). It is evident that the disease may be present for years before a diagnosis is made (*see* M.G., Table 5—twenty-two years) and that it is not uncommon for the patient's condition to be good ten years after the diagnosis (*see* L.F., V.G. and M.S., Table 5).

TABLE 5. LIFE CYCLE OF CARCINOMA OF THYROID

Patient	Age (yrs.)	Type of Carcinoma	Estimated duration of neoplasm before diagnosis	Treatment	Time patient living after treatment	Total time since diagnosis	Progress
E.H.	*32** 31†	Alveolar 1st; papillary 2nd	7 yrs.	Surgery 1951; 30 millicuries I^{131}	1 yr.	8 yrs.	Condition good; no recurrence
E.A.	21	Papillary 1st; follicular 2nd	6 yrs.	Surgery 1951	1 yr.	7 yrs.	Condition excellent; no recurrence
L.F.	*53* 56	Malignant adenoma	41 yrs.	Surgery 1948	4 yrs.	45 yrs.	Excellent condition; no known metastases
V.G.	*29* 27	Adenocarcinoma, grade 2	8 yrs.	Surgery 1949; 2 operations	3 yrs.	11 yrs.	Good condition; no recurrence
M.S.	*33* 45	Adenocarcinoma, Hürthle-cell type	4 yrs.	Surgery 1940 and 1952	11 yrs.	15 yrs.	Condition good
M.B.	*69* 77	Hürthle-cell type	5 yrs.	Surgery 1945; X-ray therapy	7 yrs.	12 yrs.	Condition only fair; pulmonary fibrosis; few small nodules left neck
M.G.	*70* 77	Papillary	22 yrs.	Surgery 1945 and 1950	7 yrs.	29 yrs.	Condition bad; pulmonary fibrosis & myocardial degeneration; coronary
J.K.	*78* 80	Hürthle-cell type	17 yrs.	Surgery 1950	2 yrs.	19 yrs.	Severe lumbo-arthrosis; no evident metastasis
C.H.	*30* 31	Papillary	6 mos.	Surgery 1950; 90 millicuries I^{131}	2 yrs.	2½ yrs.	Condition good; no recurrences
M.L.	*5* 6	Papillary 1st; alveolar 2nd	1 yr.	Surgery 1951; 2 operations	1 yr.	2 yrs.	Condition good; no recurrence; tracheotomy tube
R.E.	*52* 54	Malignant lymphoma	2 mos.	Surgery 1949; X-ray therapy	3 yrs.	3 yrs. 2 mo.	Condition good; no evident recurrences
G.E.	*27* 30	Adenocarcinoma, grade 3	6 mos.	Surgery 1948	4 yrs.	4½ yrs.	Condition good; no metastases

* Age at time of microscopic diagnosis.
† Age when first seen by us.

TREATMENT

The principal problem in the treatment of metastatic thyroid cancer is the destruction of the metastases with radioactive iodine. The majority of these are nonfunctioning. Several methods have been used to stimulate these metastases to increased activity:

1. Removal of all thyroid tissue, *i.e.*, induction of hypothyroidism (2).

2. Suppression of iodide uptake by means of large doses of thiouracil, in order to induce a more profound myxedema (3).

3. Stimulation by thyrotropic hormone (4).

Before the metastatic lesions are treated with radioactive iodine, all thyroid tissue should be removed surgically and any accessible metastases removed. If the tumor recurs locally, as much as possible should be removed surgically. There are a few exceptions to this rule: 1) when a patient has some complication from the previous surgical procedures, such as recurrent nerve injury or tetany, 2) when there are cardiac or other contraindications. Under these circumstances, the thyroidectomy should be completed by the isotope. Twelve cases were treated in this manner, using 10 to 50 millicuries of radioactive iodine.

The amount of radioactive iodine which is used to complete the thyroidectomy should not be counted as a therapeutic dose. As long as any thyroid tissue is present, the metastases have little chance to become hyperplastic and function, *i.e.*, metabolize radioactive iodine. The result is that the metastatic lesion will receive no radioactive iodine under these conditions.

Fourteen patients were hypothyroid after initial surgery but in none of these was there an increased uptake of tracer doses of radioactive iodine or a significant retention of the isotope as indicated by analysis of the urine (Table 6). Of these 14 patients, 6 are deceased (1 death due to an auto accident).

These results were so discouraging that we initiated the method of attempting to stimulate the metastatic lesions with thyrotropic hormone while the patients were taking desiccated thyroid or *l*-thyroxine.

The regimen adopted for the remainder of the series was as follows:

1. Surgical removal of accessible thyroid gland and metastases, and complete destruction by the isotope of the remaining inaccessible thyroid tissue.

2. X-ray survey to locate other metastases.

3. Administration of desiccated thyroid or of *l*-thyroxine in order to maintain a constant state of euthyroidism, as estimated by the clinical condition of the patient and serial determinations of serum protein-bound iodine concentration.

4. Tracer studies with radioactive iodine to establish any collection of the isotope in the thyroid or other parts of the body; and determination of the 72-hour urinary excretion of the tracer.

5. Intramuscular or intravenous administration of TSH (Armour's or Parke, Davis)—15 milligrams twice a day for five to six days.

6. Repetition of tracer studies with radioactive iodine (second dose) to establish any improvement in the collection of the isotope or reduction in the excretion of the tracer.

7. If significant increase of retention is found, as indicated by higher

TABLE 6. FOURTEEN PATIENTS MAINTAINED IN THE HYPOTHYROID STATE

Patient	Type of Carcinoma	Serum PBI (γ/100 cc.)	Thyroidal uptake of I^{131} (%)	Urinary excretion of I^{131} (%)	Progress
R.H.	Papillary	—	0, 1, 0.14	81	Total thyroidectomy, 1946, 1949. Condition good, no recurrence
A.G.	Small-cell carcinoma; areas of Hashimoto's dis.	1.0	1		General condition good; no recurrence. Surgery, 1949.
D.S.	Follicular and papillary	1.5	Thyroid, 0; Lft. lobe, 5, 11	91 81	Surgery 1952. Condition good; no recurrence.
R.M.	Papillary	2.7	10, 12.8		Condition fair; no recurrence at time of accidental death in auto accident.
M.G.	Papillary	0.5	2.9		Surgery 1945, 1950. Condition bad; pulmonary fibrosis, and myocardial degeneration.
C.H.	Papillary	2.2	1, 0.8		Surgery 1950; 90 millicuries I^{131}. Condition good; no recurrence
J.G.	Papillary	2.3	0.6, 0.3	90.8	Surgery 1949; 10 millicuries I^{131}. Condition good; no recurrence.
W.L	Papillary	2.8	3		Surgery; no metastases.
R.P	Papillary	3.7			Surgery 1941, 1945 and 1947. Died 1951; pulmonary metastases.
V.B.	Papillary	2.6	10	92	Gradual downhill course. Died March 27, 1951; no autopsy.
A.W.	Follicular, anaplastic	1.0	Thyroid, 16; Sternum, 5%		No surgery. Died May 28, 1951; metastases lungs, pleura, adrenal and abdominal lymph nodes.
G.N.	Papillary	0.5	0, 2.1		Surgery 1927, 1949. Died Jan. 23, 1952; recurrence in neck
B.C.	Papillary	1.3	0		Surgery 1949. Died May 16, 1950; metastases to both lungs.
G.W.	Papillary	1.2	8		Surgery 1950; 93 millicuries I^{131}. Condition bad; cardiac failure with pleural effusion.

surface gamma-radiation or decreased radioactive iodine excretion, the immediate administration of a therapeutic dose of radioactive iodine, usually of the order of 100 millicuries.

8. If no change in the uptake or retention of radioactive iodine is found, continuation of thyroid medication and repetition of the study in six months.

Thirteen patients have been studied by the foregoing method. Two are deceased. Three showed an improvement sufficient to warrant giving a therapeutic dose of radioactive iodine. Ten patients showed no improvement (Table 7).

Clinical Examples

Case #1, N.B., white, married female, aged 21 (Figs. 1–4). Tumor appeared in the right lobe of the thyroid during her first pregnancy two years previously, in September 1951. She was delivered of a normal child, which was nursed for three weeks. A tumor appeared in the left lobe of the thyroid in May 1952, during the first trimester of her second pregnancy. At the end of the second trimester, October 31, 1952, a right total lobectomy and a radical left subtotal thyroidectomy were performed, for bilateral anaplastic carcinoma of the thyroid. Re-exploration of the left neck one month later revealed no thy-

TABLE 7. TSH STUDIES

Patient	Serum PBI (γ/100 cc.)	Uptake of I^{131} before TSH (%)	Urinary excretion of I^{131} before TSH (%)	TSH (15 mg., 2×dy.)	Uptake of I^{131} after TSH (%)	Urinary excretion of I^{131} after TSH (%)	Pathology
R.R.*	4.2	Thyroid, 0 Sternum, 1.3 Hip, 0	96	4 days, i.v. 5 days, i.m.	Thyroid, 3 Sternum, 14 Hip, 4	79	Follicular solid
				14 days, i.m.	Thyroid, 0.9 Sternum, 11 Hip, 0		
E.E.*	5.1	Thyroid, 0 Skull, 7	64	9 days, i.m.	Thyroid, 2 Skull, 18	Inconclusive	Follicular & alveolar
R.H.	5.6	Thyroid, 0.14	64.1	7 days, i.m.	Thyroid, 0.14	81.5	Papillary & alveolar
M.L.	5.3	Thyroid, 0.5	90.2	7 days, i.m.	Thyroid, 1.9	85	Papillary & follicular adenocarcinoma
D.S.	6.6	Thyroid, 0	91.5	10 days, i.v.	Thyroid, 0.6	91	Follicular & papillary
I.C.	4.0	Thyroid, 1.3	58	6 days, i.m.	Thyroid, 2.2	59	Papillary & follicular adenocarcinoma
J.G.	2.3	Thyroid, 0.3	90.8	6 days, i.m.	Thyroid, 0.19	88.8	Papillary adenocarcinoma
G.R.	4.0	Thyroid, 0	74	5 days, i.m.	Thyroid, 0	50	Adenocarcinoma simplex
G.A.	—	Thyroid, 13 Pelvis, 0	68	8 days, i.m.	Thyroid, 47 Pelvis, 0	11.7	Follicular
G.N.	3.0	Thyroid, 4	73	6 days, i.m.	Thyroid, 3	78	Papillary adenocarcinoma
M.W.	6.0	Thyroid, 0.2	100	6 days, i.v. 4 days, i.m.	Thyroid, 0.3	44	Solid & papillary
M.D.*	4.5	Thyroid, 1.6 Nodule (see Case #2), 0.7 Spine, 2.9	100	4 days, i.m.	Thyroid, 0.8 Nodule, 28 Spine, 34	21.2	No surgery
				3 days, i.m.	Thyroid, 20 Spine, 30	1	
N.B.	—	Neck, 0.73 Rt. neck, 0.09 Lft. neck, 0.40 Rt. hip, 0.74 Lft. rib, 0.71	95.5	6 days, i.m.	Neck, 0.3 Rt. neck, 0.25 Lft. neck, 0.60 Rt. hip, 1.3 Lft. rib, 0.4/	92.4	Solid & follicular
				7 days, i.v.		91.66	

* Increase of isotope uptake and retention.

roid tissue. Postoperatively, the anterior cervical field was treated by x-ray irradiation (4,375 r in eighteen days). She was started on 2 grains of desiccated thyroid daily. During the ninth month of pregnancy, pain in the left chest occurred, and x-ray examination

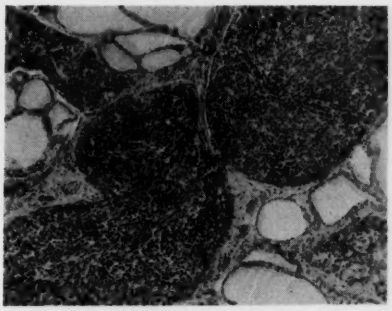

FIG. 1. *Case #1, N.B.* Surgical specimen—solid and follicular. The predominant picture is solid adenocarcinoma in the vessels of interacinar position.

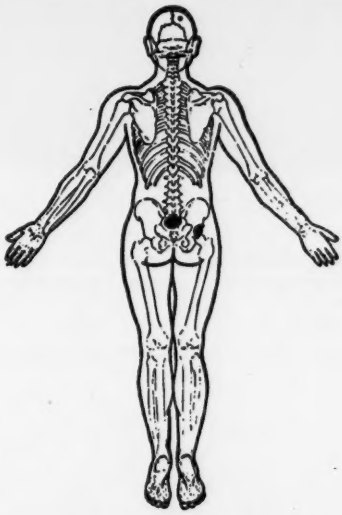

FIG. 2. *Case #1, N.B.* Location of metastases: left seventh rib, sacrum, and right ilium.

revealed bone lesions in the left seventh rib and right ilium. Subsequent films showed bone lesions in the sacrum and calvarium, and a suspicious shadow in the left lung field. February 6, 1953, two months before being seen by us, she was delivered of a normal girl. On February 24 the thyroid medication was increased to 3 grains daily. On March 3, a 72-hour urine collection, after a 100-microcurie tracer dose of radioiodine, contained 95 per cent of the administered radiation. Intramuscular injections of Parke, Davis aqueous thyrotropic hormone, 15 milligrams twice daily, were given from March 2 through March 8. The second tracer dose was given on March 9. The urine of March 10, 11 and 12 contained 92 per cent of the second tracer. Hence, no therapeutic dose was given. She was continued on 3 grains of thyroid daily. A continuous intravenous drip of Armour's lyophilized thyrotropic hormone preparation, 10 U.S.P. units (25 to 30 milligrams) daily, was given for one week, March 19 to March 26. Urine of the last three days contained 92 per cent of the administered tracer dose.

FIG. 3. *Case #1, N.B.* X-ray film of right ilium, showing large lesion, and skull of fetus.

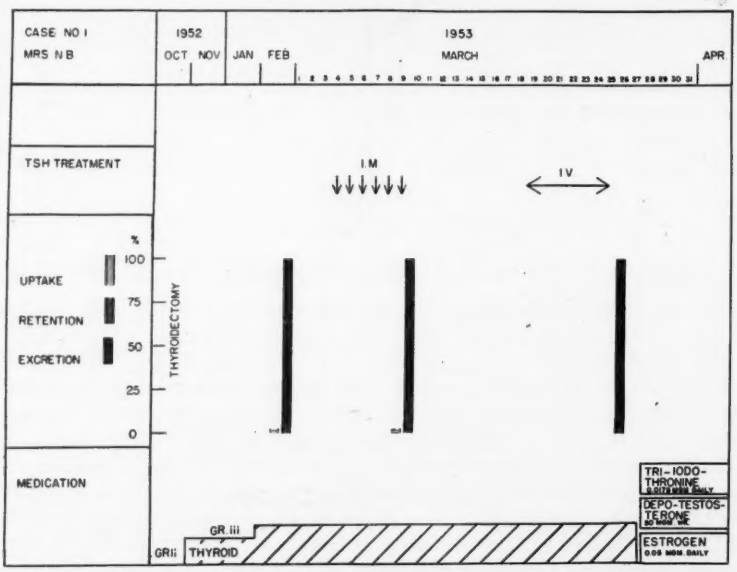

FIG. 4. *Case #1, N.B.* Uptake and retention of radioiodine before and after intramuscular and intravenous Armour's lyophilized TSH, showing lack of effect.

Case #2, M.D., a woman aged 63 (Figs. 5, 6 and 7). A nodule in the thyroid was observed twenty years before, *i.e.*, at the age of 43. She had been born in an endemic goiter area (Michigan) and hence the presence of cancer was not expected. She enjoyed good health until five years before, at which time she complained of nervousness, weakness and weight loss. A thyroidectomy had been performed in 1947, after which she was told by letter that she had a cancer of the thyroid and was given x-ray treatment. Due to metastasis in the lumbar vertebrae, arthritic back pain developed, which was aggravated by motion. Radioactive iodine was administered at a neighboring hospital in 1950, following which there was a downhill course, with weakness and partial paralysis of the legs and 40 pounds weight loss.

On physical examination she was an anemic, weak, elderly woman, with a temperature of 100° F., a pulse of 110, and a blood pressure of 200/100. There was no exophthalmos. In the thyroid area there was a well healed scar and a 1-cm. nodule at the sternal notch. She refused a biopsy. X-ray studies showed lesions in the cervical and lumbar spines.

On September 17, 1952, a tracer dose of 200 microcuries of radioactive iodine was given. The uptake over the thyroid area was 1.6 per cent; over the nodule, 0.7 per cent; and over the lumbar spine, 2.9 per cent. The 48-hour urinary excretion was recorded as over 100 per cent—an obvious technical inaccuracy. Three daily intramuscular injections of 15 milligrams of Parke, Davis aqueous TSH were given, and a second tracer of 200 microcuries was administered at the end of this treatment. Uptake over the thyroid area was 0.8 per cent; over the nodule, 28 per cent; and over the spine, 34 per cent. A 48-hour excretion showed only 21.2 per cent. This remarkable retention was doubted and the test was repeated ten days later with complete corroboration. Subsequent courses of TSH are shown in Figure 7. Treatment was withheld in February and March, 1953, because of severe anemia. Improved retention continued and, with gradual improvement in her hematologic picture, the final treatment was given on March 7, 1953.

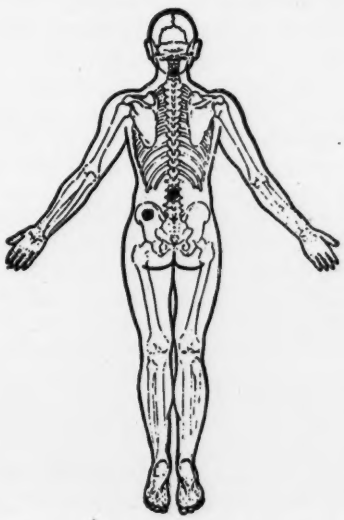

FIG. 5. *Case #2, M.D.* Location of metastases in cervical and lumbar spines and left ilium.

FIG. 6. *Case #2, M.D.* X-ray film of lesions in cervical and lumbar spines.

The radioiodine tests before administration of TSH in this case gave completely incorrect evidence of the accessibility of the cancer to internal radiation therapy. The administration of the hormone proved that isotope treatment was possible.

Case #3, J.G. (Figs. 8 and 9). This young woman was 33 years old. At 26 years of age, a lump appeared in her neck, which was thought to be a cyst. The basal metabolic rate was low. She was started on 1½ grains of desiccated thyroid daily. This was continued during her first pregnancy, which was terminated by a normal delivery on January 12, 1948. In November 1948, enlargement of the goiter occurred and a second mass in the neck appeared. A thyroidectomy was performed on February 25, 1949, at which time a diagnosis of papillary adenocarcinoma of the thyroid with metastases to the regional lymph nodes, was made. She was given fifteen x-ray treatments over the area. On June 23, 1949, she was given 10 millicuries of radioactive iodine, at which time an autoradiogram of two excised cervical lymph nodes was made. A second pregnancy occurred in the summer of 1949. It was terminated by a normal delivery on June 25, 1950. Since then, she has been taking Proloid, 3 grains, and at present 4 grains daily. Tests of retention of radioactive iodine after TSH treatment are shown in the Figures 8 and 9. It will be noted that there was practically no uptake or retention.

Case #4, R.R., (Figs. 10, 11, 12 and 13), was a 47-year-old woman with a large nodular nontoxic goiter of twenty-three years' duration. A rapid increase to double the previous size occurred from 1943 to 1944, leading to subtotal thyroidectomy. At this time, adenocarcinoma of the thyroid with blood vessel invasion was found. No record

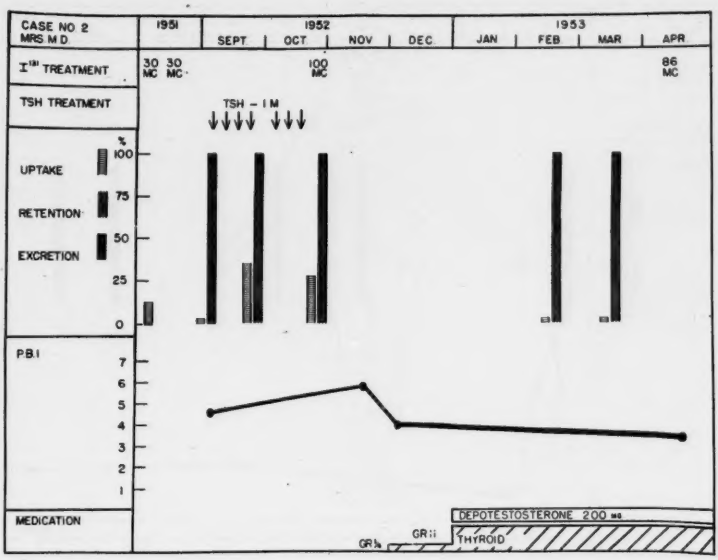

FIG. 7. *Case #2, M.D.* Marked increase of uptake and retention of radioiodine indicated after 15 mg. of aqueous TSH intramuscularly. Persistence of considerable retention without TSH treatment.

was then given for the succeeding five years, until she entered the hospital with a fractured left hip in 1949. X-ray examination showed solitary cystic destruction of the left femur, lesions in the ischium, right humerus and manubrium, and a questionable mass in the left lung. Biopsy of the lesion in the manubrium and in the subtrochanteric area of the left femur showed a follicular solid type of carcinoma. The first dose of radioactive iodine was given on November 10, 1949, since which time she has received an additional 735 millicuries, as shown in Figure 13.

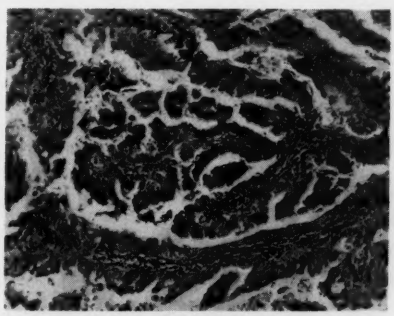

FIG. 8. *Case #3, J.G.* Surgical specimen—Papillary and alveolar. The predominant pattern is papillary.

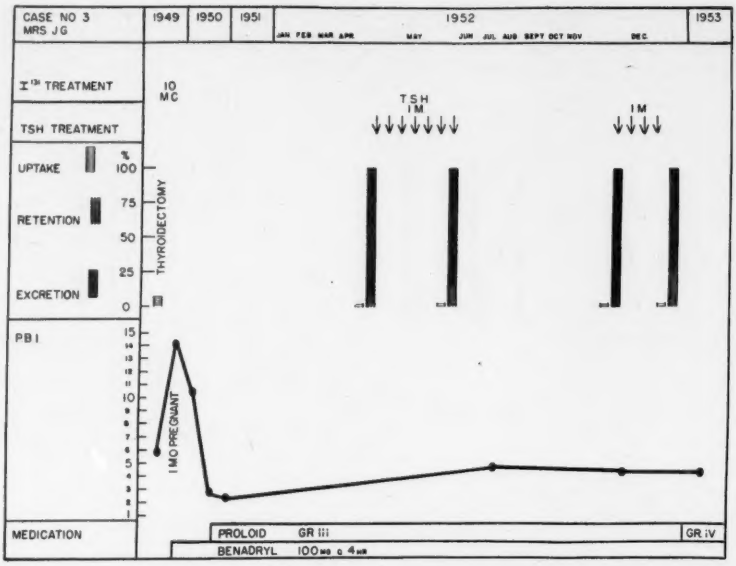

FIG. 9. *Case #?, J.G.* No significant increase in retention of radioiodine after intramuscular administration of TSH.

Improvement in uptake of radioiodine over the thyroid area and particularly over the manubrium and left hip was demonstrated after the administration of Armour's aqueous TSH for four days intravenously and for four days intramuscularly. The pre-treatment uptake over the manubrium was 1.3 per cent and over the hip, 0 per cent; after treatment the uptake over the manubrium was 14 per cent and over the hip, 4 per cent. A decrease in 48-hour urinary excretion from 96 per cent before treatment to 79 per cent after treatment was observed. At the present time, her general health is good and she is ambulatory, with a brace on the left leg. Severe anemia and leukopenia developed during

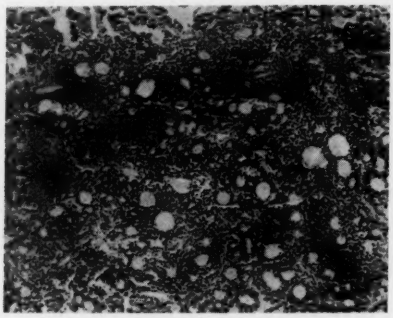

FIG. 10. *Case #4, R.R.* Surgical specimen—Follicular and solid. Needle biopsy. The predominant pattern is follicular.

FIG. 11. *Case #4, R.R.* Location of metastases in left femur, sacrum, ilium, sternum, rib and right humerus.

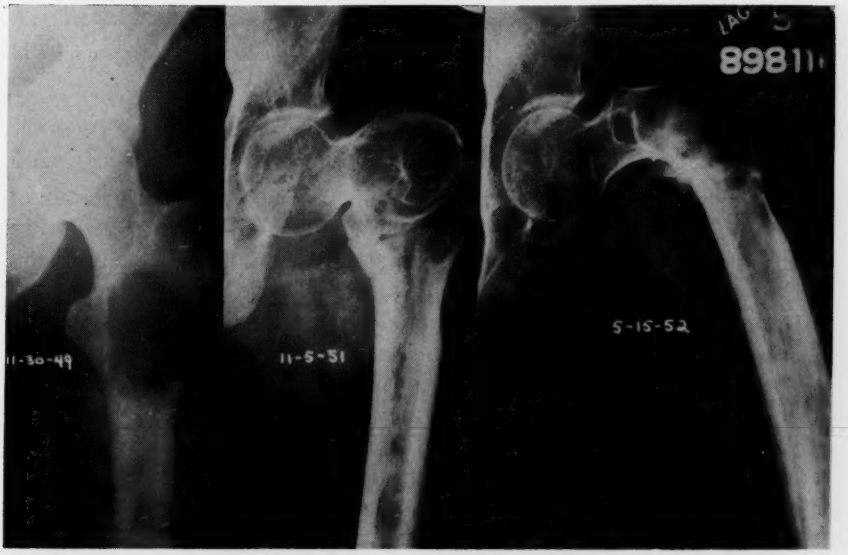

FIG. 12. *Case #', R.R.* Progressive changes in lesion of left femur during therapy starting in 1949.

radiation, from which she has recovered. She has no pain, is able to do light housework, and no new lesions have developed. She is at present receiving 0.4 milligram of sodium-*l*-thyroxine (Baxter) daily and 200 milligrams of Depo-testosterone (Upjohn) weekly.

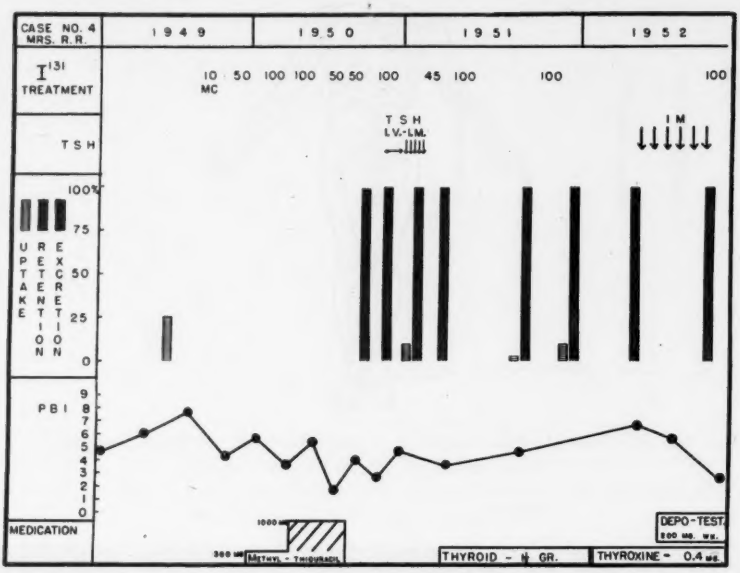

FIG. 13. *Case #4, R.R.* Increase in retention of radioiodine after intravenous and intramuscular administration of TSH. Second course of TSH in 1952 produced no significant improvement.

DISCUSSION

Of this series, there are 17 living patients under 50 years of age. Six of these have had demonstrable metastases; the remainder are not known to have disseminated tumors. These patients are a challenge to our group, and they require continual follow-up and retesting. That the euthyroid state is being maintained by adequate thyroid medication can only be shown by frequently repeated determinations of the serum protein-bound iodine level. The patient without local recurrence or scattered lesions demonstrable by x-ray examination may still have cancer growing in the body. Such patients, maintained on thyroid medication in order to suppress endogenous TSH, should be periodically tested for improvement of uptake and retention of radioiodine. Case #3, J.G., is a good example of this procedure. The complete failure of radioiodine localization (uptake) and retention *before* TSH stimulation should not be accepted as final evidence, since good retention may occur after TSH treatment. Case #2, M.D., illustrates this point. Neither Case #2 (M.D.) nor Case #4 (R.R.),

both showing good retention of the isotope, have had definitive treatment. In each case anemia developed to a point that was a serious limitation to adequate destruction of the growth. Repeated TSH treatment and testing for radioiodine retention will be carried out in the patients who have lesions but no retention, such as Case #1, N.B.

Years of observation of individual patients will be required before the value of the regimen will be learned. Whether or not a tumor which seems to resist stimulation by thyrotropic hormone will later change and become sensitive to the hormone, is at present unknown. It is evident that the dose, quality and rate of administration of the thyrotropic hormone is in need of study. The experience with ACTH in the stimulation of the adrenal gland indicates that preparations of much higher potency and more prolonged effectiveness can be developed. The objection might be raised that the administration of thyroid hormone, calculated to slow the rate of growth of the cancer, may actually delay the metamorphosis of the cancer to a form which will attract the isotope. This remains to be seen. The education of the attending physician and particularly of the patient is essential for the successful performance of this plan of treatment.

SUMMARY

A series of 50 patients with cancer of the thyroid has been analyzed. Of these, 14 treated with radioactive iodine during induced hypothyroidism showed no evidence of retention of the isotope.

A regimen of maintained euthyroidism was established by means of thyroid hormone therapy in a series of 13 patients. Among these, 4 showed a retention of a therapeutic dose of radioactive iodine after treatment with thyrotropic hormone. Four illustrative cases are presented in detail.

The hypothesis is suggested that, by suppression of endogenous TSH, the growth of the cancer and the occurrence of metastases may be retarded.

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THE PRESENT-DAY PROBLEM OF CANCER OF THE THYROID*

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RECENT experiences in the surgical management of a large number of patients with thyroid disease have emphasized the fact that carcinoma of the thyroid is being seen more frequently and its treatment has been undergoing needed changes in order to improve the end results. In spite of the fact that a considerable number of patients are seen who have a relatively low grade of thyroid malignancy, many are encountered with extensive malignant involvement leading to early death in spite of the best recognized combined surgical and radiation treatment. For those physicians who see relatively few thyroid patients the problem of carcinoma of the thyroid may not seem important, but as a result of a considerable experience at the Lahey Clinic in the treatment of carcinoma of the thyroid, questions have arisen which we believe could be clarified by a review of recently treated patients. For example, in what percentage of cases can a clinical diagnosis of carcinoma of the thyroid be made? Can carcinoma of the thyroid exist without signs or symptoms? Is carcinoma of the thyroid increasing in frequency? What is the present incidence of carcinoma in discrete nodules and in diffuse nodular goiter? Has there been an appreciable increase in papillary tumors? What changes in surgical treatment have occurred? Should the number of radical neck dissections be increased?

In the hope of throwing some light on these and other questions we thought it would be worth while to review our experiences in the surgical treatment of a considerable number of patients operated upon during the last two years. We have reviewed the records of all patients with carcinoma of the thyroid treated in 1951 and in 1952. This comprises a consecutive series of 78 cases of carcinoma of the thyroid. The diagnosis was established histologically in all instances by Dr. Shields Warren, Dr. William A. Meiss-

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ner and their associates. During this two-year period 1,479 patients were operated upon for thyroid disease. Thus, 5.3 per cent of all thyroid operations during this time were performed for carcinoma of the thyroid.

The types of goiter, verified by the pathologic study, are listed in Table 1. There were 447 patients with primary hyperthyroidism or exophthalmic goiter. Although in an occasional case of primary hyperthyroidism a small focus of carcinoma is found, none was encountered in this group. In

TABLE 1. THYROID DISEASE—1951 THROUGH 1952

(1,479 cases)	
Nontoxic adenoma	104
Nontoxic multiple colloid adenomatous goiter	644
Toxic multiple colloid adenomatous goiter	113
Primary hyperthyroidism	447
Thyroiditis	93
Carcinoma	78
Total	*1,479*

the past, such cases have been demonstrated to be of a very low grade of clinical malignancy and carcinoma has not recurred following thyroidectomy in any case. An occasional case may show invasive malignancy in association with thyroiditis, usually of the Hashimoto type, but none was encountered among the 93 patients with thyroiditis who were seen during this two-year period. A discrete single adenoma of either the fetal or follicular type was found in 104 patients. Diffuse nontoxic nodular goiter (multiple colloid adenomatous goiter) was seen more than six times as frequently as the discrete adenoma, and occurred in 644 patients. Diffuse nodular goiter associated with secondary hyperthyroidism was found in 113 patients.

The incidence of thyroid carcinoma in this series in relation to discrete nodular and diffuse nodular goiter is shown in Table 2. Carcinoma was found in 76 patients among the 748 with nontoxic nodular goiter—an incidence of 10.2 per cent. Two patients with invasive malignancy were encountered in 113 patients with toxic nodular goiters, or 1.8 per cent. Thus the over-all incidence of thyroid carcinoma in relation to nodular goiter was 9.1 per cent over this two-year period.

This incidence of malignancy of 9.1 per cent in all cases of nodular goiter is somewhat higher than has previously been reported in the literature. The figure reported by Pemberton (1) and by Black (2) for the period 1907 to 1947 was 4.8 per cent. In other series Brenizer and McKnight (3) reported 4 per cent; Horn and associates (4), 6.3 per cent; Crile (5), 5.6 per

cent; and Ward (6), 4.8 per cent. The higher incidence that we found may be due to the fact that all nodular goiters, both discrete and diffuse, were included. Another factor that may be important is that a number of patients were referred to the clinic with the diagnosis of carcinoma of the thyroid already established. Our own figures, however, seem to indicate an increased incidence of thyroid malignancy in nodular goiter during this recent period.

Carcinoma of the thyroid occurs in younger patients than is the case with many epithelial malignancies. Of the 78 patients in this series, 5 were under 20 years of age, and 5 were between 20 and 30 years; 48 (more than

TABLE 2. THYROID DISEASE—1951 THROUGH 1952: INCIDENCE OF THYROID CARCINOMA IN RELATION TO NODULAR GOITER

Type	No. of cases	Carcinoma	
		No.	Per cent
Nontoxic nodular goiter	748	76	10.2
Adenoma 104			
Multiple colloid adenomatous goiter 644			
Toxic nodular goiter	113	2	1.8
Total—Nodular goiter	*861*	*78*	*9.1*

one-half) were under 45 years of age. In the older age group, carcinoma simplex was the most frequent histologic type.

The sex incidence was the same as in other thyroid diseases, with 21 males and 57 females, a ratio of 3 to 8. The right and left lobes of the thyroid showed an equal incidence of malignant involvement.

There are no diagnostic signs or symptoms of carcinoma of the thyroid in the early stage of its development. A high index of suspicion must be maintained for any nodular enlargement of the gland. It should be suspected, moreover, whenever the gland has increased rapidly in size or whenever the gland is hard and irregular. The fact that a clinical diagnosis is not established in a majority of cases is borne out by this series (Table 3), since the diagnosis of carcinoma was definitely made or suspected in less than one-half of the cases in which it was found later. In 52 of the 78 patients with proven carcinoma a diagnosis of discrete adenoma was made, and in only 15 of these was a question of carcinoma included in the preoperative diagnosis. A diagnosis of diffuse nodular goiter was made in 13 cases; 11 of these were thought to be nontoxic and only 1 was suspected of being carcinoma. Two additional patients had diffuse nodular goiter with

hyperthyroidism. In 11 patients carcinoma of the thyroid was apparent clinically.

The incidence of carcinoma in what appears on clinical examination to be a solitary adenoma, is very difficult to determine. In 52 patients in this group who were operated upon, the preoperative diagnosis was discrete or solitary adenoma but all proved to have carcinoma. During this same two-year period 104 patients were operated upon for discrete adenoma which proved to be benign. The total of 156 solitary nodules found during this two-year period represents all of the true solitary adenomas encountered in the series of 1,479 patients. Thus the incidence of carcinoma in the group of 156 patients with solitary nodules is 33.3 per cent. This figure is considerably higher than Crile's 24.5 per cent (5), Ward's 15.6 per cent (6),

TABLE 3. CARCINOMA OF THE THYROID—1951 THROUGH 1952: CLINICAL DIAGNOSIS

(Carcinoma suspected in less than half.)	
Adenoma	37
Adenoma ? carcinoma	15
Cervical adenitis	1
Multiple colloid adenomatous goiter	10
Multiple colloid adenomatous goiter—? carcinoma	1
Multiple colloid adenomatous goiter—with hyperthyroidism	2
Thyroiditis	1
Carcinoma	11
Total	*78*

Cole's 24.4 per cent (7), and Cope and associates' 19 per cent (8). In a large series reported from this clinic by Lahey and Hare (9) and by Meissner and Lahey (10) the incidence of carcinoma in solitary nodules was found to be 10 per cent. Undoubtedly some of the patients seen during this two-year period whose clinical diagnosis was solitary adenoma proved on pathologic examination to have a multiple colloid adenomatous goiter. Thus they could be included in the group of 644 patients with this diagnosis, and the incidence of carcinoma in patients with a "*clinical*" impression of a single adenoma would be less than 33 per cent. This estimate is at least partially offset by the fact that some of the 13 cases of carcinoma diagnosed clinically as diffuse nodular goiter, and some of the 11 cases diagnosed clinically as carcinoma, may have appeared to have a discrete nodule early in the clinical course.

The fact remains that in this two-year period the incidence of carcinoma in nodular goiter, single or multiple, was at least 9.1 per cent. When this figure is compared with the over-all incidence of carcinoma in nodular goiter of 4.4 per cent reported by Lahey and Hare in the earlier series re-

ferred to, it adds support to our belief that the incidence of thyroid carcinoma is increasing.

A pre-existing goiter was present in 58 of our 78 cases of carcinoma of the thyroid. The goiter had been present for over five years in 25 cases and for over a year in more than half the cases. Many of these patients with long-standing goiter had been advised that operation was not indicated because symptoms were absent. In 9 patients the goiter was discovered on routine physical examination.

Because the clinical diagnosis of malignant disease of the thyroid is so difficult to make, as is shown in this series of cases, it becomes essential to advise the removal of all discrete nodules of the thyroid in patients of any age and to advise thyroidectomy for a diffuse nodular goiter that shows any appreciable increase in size in addition to other indications for surgery.

The type of neoplasm encountered is shown in Table 4. Four were con-

TABLE 4. CARCINOMA OF THE THYROID—1951 THROUGH 1952: PATHOLOGY

Malignant adenoma	4
Papillary	37
Alveolar (follicular, adenocarcinoma)	19
Simplex, small-cell, giant-cell	18
Total	*78*

sidered of low-grade malignancy but showed blood vessel invasion and invasion of the capsule of the adenoma. In 37 patients the papillary elements predominated. This group represented almost half of the series. There were 19 cases of alveolar carcinoma, including follicular or adenocarcinoma, as well as two Hürthle-cell tumors. Small-cell and giant-cell tumors were included in a group of 18 cases of carcinoma simplex. These two types of carcinoma simplex were equally divided.

In the surgical treatment of advanced carcinoma of the thyroid in which the clinical diagnosis is assured, biopsy is performed in order to determine the cell type. Most of these growths are carcinoma simplex. When all of the gland is involved by this type of malignancy, often associated with invasion of the adjacent muscles, as complete a thyroidectomy as is technically possible is carried out, with removal of the prethyroid muscles, the deep cervical fascia and, at times, portions of the sternomastoid muscles. Because of the frequent occurrence of postoperative respiratory obstruction due to laryngeal edema, and the occasional occurrence of a temporary paralysis of one cord, tracheotomy is usually advisable before the procedure is completed. When invasion is extensive, with involvement of the mediastinum, and thyroidectomy is not feasible, an attempt is made to

clear the trachea and perform a tracheotomy, relying upon roentgen therapy for palliation.

In the majority of cases of cancer of the thyroid the diagnosis is not suspected preoperatively. This makes it advisable to have facilities for frozen section available for all cases of nodular goiter. If signs of invasion or extension are found at operation, a biopsy enables the surgeon to plan the operative procedure at that time. In view of the high incidence of malignancy in discrete nodules, simple enucleation of the adenoma is not justified. If there are no clinical signs of malignancy and no operative findings to suggest it, subtotal hemithyroidectomy is indicated. Frozen section is imperative in any instance in which there is a suspicion of carcinoma and might well be carried out in all cases of adenoma. If on exploration of the

TABLE 5. CARCINOMA OF THYROID—1951 THROUGH 1952: SURGICAL TREATMENT

Excision	7
Subtotal hemithyroidectomy	5
Total lobectomy	9
Bilateral subtotal thyroidectomy	6
Total thyroidectomy	3
Total lobectomy and subtotal hemithyroidectomy	3
Biopsy	7
Radical neck dissection	38
Total	*78*

neck there are suggestive findings, total lobectomy should be proceeded with and the entire lobe submitted to the pathologist for frozen section.

If malignant disease has not been suspected in a discrete nodule the patient may not have been prepared for neck dissection and under such conditions total lobectomy can be performed and the neck dissection delayed for a few days. When malignancy is suspected, the possibility of radical neck dissection should be discussed with the patient before operation.

The surgical procedures employed in the 78 patients with carcinoma of the thyroid treated during 1951 and 1952 are listed in Table 5. Excision or subtotal hemithyroidectomy was carried out in 12 instances, lobectomy in 9, and total thyroidectomy in 3. The lesion was so advanced in 7 cases that only a biopsy was performed. In 9 cases radical neck dissections were made along with total lobectomy at the initial operative procedure and in 29 cases the radical neck dissection was performed within a short period following the first operative procedure on the thyroid. In approximately half

of the cases, neck dissection was carried out either unilaterally or bilaterally.

There was no operative mortality. Eleven patients had tracheotomy at the time of the initial operative procedure.

Twenty-six of the 37 patients with carcinoma of the papillary type had neck dissections and, of these, the cervical lymph nodes were involved in 13—half of the cases (Table 6). Twelve of the 17 patients with carcinoma of the alveolar type had neck dissections and, again, the cervical nodes were involved in half of the cases. No neck dissections were performed for carcinoma simplex.

TABLE 6. CARCINOMA OF THE THYROID—1951 THROUGH 1952: RADICAL NECK DISSECTION

Papillary		26
Nodes involved	13	
Nodes not involved	13	
Alveolar		12
Nodes involved	6	
Nodes not involved	6	
Simplex		0
Total		*38 (50%)*

As reported by Lahey and Hare (9) we utilized roentgen therapy postoperatively in the majority of cases. During this recent period of 1951 and 1952 all patients who received x-ray therapy were given two-million volt rotational therapy at the Massachusetts Institute of Technology under the direction of Dr. John G. Trump and Dr. Hugh F. Hare. Fifty-five of the 78 patients were so treated. This therapy is recommended in all advanced cases. It was not given to some patients who had neck dissection but in whom the nodes were not involved, or to those in whom there was no demonstrable invasion of lymphatics or blood vessels on pathologic examination of the adenoma.

Although there was no operative mortality, 9 of the 78 patients are dead. Eight of these deaths occurred in patients who had carcinoma simplex and the ninth patient had alveolar carcinoma. All patients died at home and no autopsies were obtained in this group.

SUMMARY

A consecutive series of 78 patients with carcinoma of the thyroid treated at the Lahey Clinic in 1951 and 1952 is reported. During this time 1,479 patients with thyroid disease were operated on; the over-all incidence of malignancy was 5.3 per cent. One patient with carcinoma of the thyroid

was encountered for each 10 patients with discrete or diffuse nodular goiter.

The clinical diagnosis of carcinoma was made preoperatively in less than half of all patients. A high incidence of carcinoma was encountered in discrete or solitary nodules of the thyroid. There were 156 patients with this type of goiter. Carcinoma was suspected in only 15 and encountered in 52, or 33.3 per cent.

Frozen-section diagnosis should be available at the time of operation in all cases of discrete nodules and would be helpful in operations for all nodular goiters.

Neck dissection was considered necessary in approximately half of all patients with carcinoma of the thyroid operated upon during this two-year period. This procedure is indicated in any patient with a malignant adenoma which shows lymphatic invasion, in all patients with papillary carcinoma and in all patients with alveolar carcinoma. The increased use of radical neck dissection together with high-voltage x-ray therapy postoperatively may improve our end results in the treatment of carcinoma of the thyroid. In half of those patients in whom neck dissection was performed, the lateral cervical nodes were found to be involved.

Carcinoma of the thyroid is an extremely serious lesion and is frequently encountered if large numbers of thyroid patients are seen. In this series of 78 patients there was no operative mortality but 9 patients are already dead from malignancy less than two years after operation.

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BILATERAL PARALYSIS OF THE VOCAL CORDS: SYMPTOMS, DIAGNOSIS AND TREATMENT*

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THE opportunity has been afforded me to examine the larynx of a large number of patients before and after thyroidectomy. Twenty-five years ago, and over a period of approximately three years, it was my duty in connection with an active surgical service to make preoperative examinations of the vocal cords of all patients who were to undergo thyroidectomy and, ten to fourteen days later, to make corresponding postoperative examinations of the same patients. These examinations were made by indirect laryngoscopy. If a postoperative examination revealed that the patient had experienced paralysis of a vocal cord, inquiry was made regarding any untoward symptoms he might have suffered during the early postoperative days. Careful records of the replies were kept until a series of 88 such cases had been accumulated. For comparison, corresponding records for patients who had not suffered vocal cord paralysis were kept. When 1,300 such records were available, this control series was terminated.

CLINICAL ASPECTS

Analysis of the records revealed that hoarseness or choking (fluids entering trachea) or both were significant symptoms and especially so if both were present during the first three to five postoperative days. Eighty per cent of patients who had suffered vocal cord paralysis had both symptoms during the early postoperative period, whereas in the control series the combination was present in only 0.2 per cent. Therefore, it can be stated that if a thyroidectomized patient experiences both hoarseness and choking during the first five postoperative days it is highly probable that at least one vocal cord has been paralyzed.

It was observed in the course of this study that occasionally the post-

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operative examination would reveal a paralyzed vocal cord in a patient who had not had the usual early symptoms. Some of these patients had noted slight hoarseness beginning after several postoperative days, and the question arose as to whether a vocal cord might become paralyzed several days after operation. It was decided, therefore, to examine the larynx of each thyroidectomized patient within a few hours after operation, in addition to the usual examination ten to fourteen days later. This study revealed that in an occasional patient the larynx would be found to be normal immediately after operation but a paralyzed cord would be observed ten to fourteen days later. On re-examination of such patients several months later, it was observed that the paralysis had disappeared.

No explanation can be offered for the occurrence of this late paralysis but there is the possibility that it might be caused by edema within the sheath of the recurrent laryngeal nerve.

One of the surgeons whose patients were under observation during this study declined to accept the idea that there could be late paralysis of a vocal cord, until a most convincing incident occurred which involved one of his patients. The examination immediately after operation had revealed no paralysis. The patient was having an uneventful convalescence and at noon on the ninth postoperative day the surgeon had told her she might leave the hospital. Three hours later tracheotomy became necessary, owing to bilateral paralysis of the vocal cords. Examination several weeks later revealed that both vocal cords had regained normal function. I have seen no other case of late bilateral paralysis.

A knowledge of the behavior of a vocal cord after it has been paralyzed during thyroidectomy makes it easy to understand the ensuing symptoms. When a vocal cord thus has become paralyzed it of course becomes immobile[1] and almost invariably at first its medial margin is bowed outward. Gradually, over a length of time which varies from a few days to six months this outward bowing disappears and the margin of the vocal cord again becomes a straight line. The explanation for this gradual change is not known. The position which this immobile cord eventually assumes is at or near the position a normal vocal cord assumes during phonation, *i.e.*, at or near the median line of the larynx. Thus in the case of a patient who has suffered paralysis of only one vocal cord, two things are noteworthy six months or more afterward: The first is that the paralyzed cord is in good position for phonation, so that when its normal partner moves to a corresponding position the conditions for speech are essentially normal; hence the patient is not hoarse. The second is that the patient practically never

[1] For all practical purposes the paralyzed vocal cord is immobile but in a considerable percentage of cases laryngoscopic examination reveals that it does move slightly. It is not understood why this is true in some patients.

complains of dyspnea. This is because the normal airway is about twice as large as needed for normal activities and because the paralyzed vocal cord obstructs no more than one half (usually somewhat less than half) of the airway. Since, therefore, such a patient usually has neither hoarseness nor dyspnea the condition often will be unrecognized by his physician and the patient rarely will be aware that there has been any change in his vocal and respiratory apparatus.

Since paralysis of one vocal cord so easily may escape detection unless laryngoscopic examination is made, and since it does reduce the airway to one half of normal, it must be remembered that if this patient's other vocal cord should become paralyzed his half-capacity airway will suffer considerable further reduction and he then may have only one-fourth the normal capacity or even less. Such a sudden narrowing of the airway may make immediate tracheotomy necessary. This emphasizes the fact that if a patient is to have a second thyroidectomy it is very important that the larynx be examined before operation, so that the surgeon may be forewarned and forearmed if the patient already has one paralyzed vocal cord.

It is possible that some respiratory emergencies during thyroidectomy, which have been attributed to tracheal collapse, have instead been caused by paralysis of a vocal cord in a patient whose other vocal cord previously had been paralyzed.

Let us now apply the known facts regarding the behavior of the vocal cord paralyzed by surgical trauma to the course of events following the occurrence of simultaneous surgical paralysis of both vocal cords. Both vocal cords would be immobile and at first both would be bowed; hence, during the early postoperative period the patient would be very hoarse or even aphonic. There would be no dyspnea because of the ample airway between the bowed vocal cords. Also, in the early postoperative period the patient would be likely to have considerable trouble with choking because the glottis cannot be closed to keep liquids from entering the trachea. Because of this the patient might suffer from aspiration pneumonia and the first few days of the postoperative course probably would be very stormy. I have not had an opportunity to observe, during the immediate postoperative period, a patient who had experienced simultaneous surgical paralysis of both vocal cords. I have talked with numerous patients, however, who have had this disability, and their descriptions indicate that their symptoms have corresponded closely with those to be expected and as outlined above.

The bowing of the vocal cords gradually changes during a period of four to six months after the onset of bilateral paralysis, so that the margins become more nearly straight. As this change occurs, the hoarseness improves because the cords are approaching nearer and nearer to the position

which normal cords assume during phonation. Usually when the change is complete the voice is practically normal. During the same period the patient becomes increasingly dyspneic, because the previously-described change causes gradual reduction in the airway. The final degree of dyspnea will depend upon how near to the median line of the larynx the paralyzed vocal cords take their position. This varies with different patients and it is not known why there is such a variation. In some patients the space between the cords is wide enough to provide as much as 30 to 40 per cent of the normal airway, and the patient may be able to carry on quite comfortably. In most instances, however, the airway is reduced to 25 per cent of normal or less, and the patient is severely handicapped with respect to physical activities. The narrowing of the airway takes place very gradually, so that some patients adjust themselves so well that they live in reasonable comfort with an airway that is not more than 20 per cent of normal.

Patients who have bilateral paralysis of the vocal cords react badly to opiates and to barbiturates and they tolerate general anesthesia very poorly.

DIAGNOSIS

Post-thyroidectomy simultaneous bilateral paralysis of the vocal cords readily can be diagnosed simply by talking with the patient, if the condition is suspected and has existed six months or more. The chief complaint will be that of shortness of breath on exertion. Appropriate questioning will elicit the history of thyroidectomy, followed immediately by loss of voice, by several days of acute illness, and later by gradual return of and improvement in the voice, accompanied by the appearance of gradually increasing dyspnea.[2] It will be noted that inspiration is prolonged and accompanied by a low musical tone in the throat. If the physician next will ask, "Do your relatives say that you make a lot of noise when you sleep?" the reply will be, "Oh, yes—it is terrible—I even waken myself." It is a real problem both for the patient and for his relatives. One patient's primary complaint was "I want to travel but I cannot because I disturb other people so much when I sleep."

TREATMENT

Treatment for bilateral paralysis of the vocal cords is indicated whenever the degree of dyspnea is such that the patient cannot live comfortably and happily within the limitations imposed by it.

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[2] In the case of a patient who suffers paralysis of one vocal cord at one operation, and of the other cord at a later operation, the dyspnea usually appears immediately after the second procedure. The subsequent history will be similar, however, and the ultimate symptoms the same.

TABLE 1. BILATERAL PARALYSIS OF THE VOCAL CORDS: TREATMENT BY TRANSORAL ARYTENOIDECTOMY (50 PATIENTS)

Results	Patients	Remarks
Excellent	47	Six required operation on both sides
Fair	2	One happy with elimination of noisy sleeping—needs operation on other side. One writes, "better but not enough"—needs operation on other side.
Unsatisfactory	1	Previously had King operation on both sides—slight improvement.

In some cases the separation of the paralyzed vocal cords is sufficient to provide an airway that permits the patient to live comfortably with moderate restriction of physical activities; treatment should not be urged in such cases. It should be borne in mind, however, that such patients may need treatment later in life when age reduces the margin of physical reserve so that they no longer can live comfortably with their handicap. Other patients may be so severely handicapped within six months or a year after the onset of the paralysis that surgical treatment should be advised. No patient should be operated upon earlier than six months after the onset, because occasionally late recovery of vocal cord function does appear.

Patients with bilateral paralysis of the vocal cords not uncommonly suffer from thyroid and parathyroid insufficiency. Before surgical treatment is undertaken, search should be made for evidence of such complications and suitable treatment should be instituted if any deficiency is found.

It is rather generally agreed at present that the choice of treatment rests between two methods. One is a method whereby the arytenoid is removed or is anchored laterally, with the field of operation exposed through an external incision. This method, of which there are several modifications, often is referred to as the King (1) operation because Dr. King was the first to develop the plan for it. The other is a method whereby the arytenoid is removed, with the field of operation exposed by means of the suspension laryngoscope. This method is referred to as the Thornell (2) operation, after Dr. Thornell who first described it. Those surgeons who have not been trained in the use of the suspension laryngoscope will prefer the King type of operation. Those who have had such training will prefer the Thornell operation. Good results can be achieved by either method and there is no need for any quarrel between the advocates of the respective methods. The surgeon simply should select the method he best knows how to use.

My laryngologic colleagues and I immediately were favorably impressed upon learning of Dr. Thornell's operation because we long had used the suspension laryngoscope in the treatment of patients who had tumors of the larynx. We now have employed his method in the surgical treatment of 50 patients who had suffered bilateral paralysis of the vocal cords (Table 1). In 1 of these patients the paralysis was owing to acromegaly.

SUMMARY

If a thyroidectomized patient is hoarse and also suffers from choking during the first five postoperative days, it is highly probable that at least one vocal cord has been paralyzed.

Six months or more after one vocal cord has been paralyzed at thyroidectomy the patient probably will have no symptoms referable to such paralysis.

Six months or more after both vocal cords have been paralyzed at thyroidectomy the patient's voice usually will be essentially normal but he will suffer more or less dyspnea.

Treatment for bilateral paralysis of the vocal cords is indicated whenever the patient cannot live comfortably within the limitations imposed by his dyspnea.

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Teaching Clinic

DIAGNOSIS OF HYPOTHYROIDISM

THE recognition of hypothyroidism is made difficult for the physician in his office by several misconceptions. The first of these is that the term hypothyroidism refers to the pathologic condition of the thyroid gland, whereas in fact, it refers to the condition in the body created by an insufficiency of the thyroid hormone in the tissues; this may occur without pathology in the thyroid itself. Second, the physician has in mind a clinical syndrome corresponding to myxedema, which is a rather rare and extreme form of thyroid deficiency. Far more common—and requiring diagnosis—is a clinical state of hypothyroidism, without the history or physical findings associated with myxedema. Third, the average physician, unfortunately, still feels that determination of the basal metabolic rate is a diagnostic test for hypothyroidism.

The diagnosis of hypothyroidism is indicated in a very wide variety of clinical conditions, such as (a) states of fatigue, somnolence, psychasthenia, malnutrition, obesity, anemia, hypertension, edema, chronic cardiac disease, diabetes, allergy, and gastroenterologic disorders, and (b) states of pituitary insufficiency appearing as disorders of the adrenal or gonad, since pituitary secretion is so dependent upon an adequate supply of the thyroid hormone. As indicated, hypothyroidism seems to be associated with almost every degenerative or functional disorder of every system of the body. The following are examples:

Case #1, M.A.—Postpartum hypothyroidism simulating hyperthyroidism (Fig. 1). This 34-year-old Negro married woman had a premature (six months) stillbirth at 27 years of age, associated with hypertension and edema. At 29 years of age her second pregnancy was complicated by eclampsia, leading to a cesarean section. In 1951 the third pregnancy was associated with hypertension (250/150 to 170/115), and marked edema and albuminuria; cesarean section was performed July 20, 1951. After delivery, her blood pressure promptly returned to normal (118/82) and albuminuria disappeared.

On August 31, 1951, forty days after delivery, the following note was made in the Out-Patient Internal Medicine Clinic:

> "Problem of hypertension and severe toxemia with each of three pregnancies. Now on low salt diet. Physical Examination: Blood pressure—130/94, pulse 88. Skin feels very delicate and smooth, suggestive of a hyperthyroidism. Very nervous. Noticed times when she gets very nervous without obvious cause and perspires freely and has some palpitation."

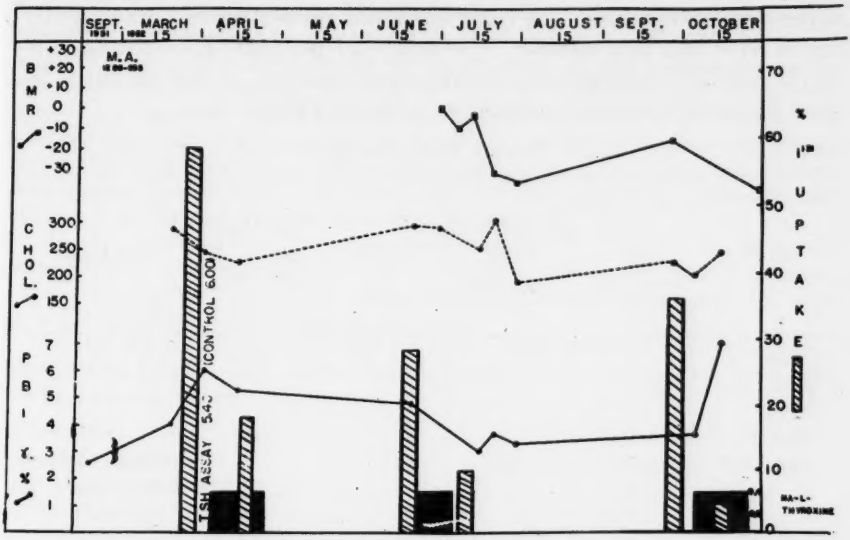

FIG. 1. *Case #1, M.A., (P.F.#1283-935).* Cross-hatched column indicates percentage thyroidal uptake of tracer dose of I^{131} at twenty-four hours (scale on the right). Dark blocks indicate daily sodium-*l*-thyroxine oral treatment in milligrams. Note reduction in height of uptake column each time thyroxine was given. Intermittent treatment was intended to promote endogenous function, but evidently failed. (Reproduced with permission from Starr, P.: Hypothyroidism. A monograph in American Lectures in Endocrinology, edited by W. O. Thompson. Springfield, Ill., Charles C Thomas, Publisher (in press).)

A serum protein-bound iodine determination was ordered which, on September 7, forty-nine days after delivery, showed 2.6 micrograms per 100 ml. On August 1, 1951, the serum A/G ratio was 3.0/2.8 grams per cent.

In March 1952, nine months after delivery, while still on a low-salt (not strict) diet, she had no complaints except that her menses were irregular, the interval being from three to four weeks with seven days of heavy flow. Blood pressure was 130/80; the urine showed sp. gr. 1.025 with 0.5 per cent albuminuria; and the blood count was normal.

On March 26, 1952, the serum protein-bound iodine level was 4.1 micrograms per 100 ml.; cholesterol, 238 milligrams per 100 ml.; and 24-hour thyroidal uptake of radioactive iodine, 59.5 per cent. The thyroid was palpable and enlarged, weighing about 40 grams. Bio-assay of the patient's serum for TSH gave negative results, *i.e.*, the MACH (mean acinar cell height) in the control tadpole was 6.00 microns, and the MACH in the patient-serum treated tadpole was 5.46 microns.

Comment: This is a most important case. As shown in Table 1, the low serum protein-bound iodine values before treatment (2.6 and 4.1 micrograms per 100 ml.) were corroborated by the three low values after treatment (3.0, 3.6 and 3.2 micrograms per 100 ml.). Hence, a state of hypo-

thyroidism was present. The basal metabolic rates after withdrawing thyroxine were also low, namely, −31 and −37 per cent. Evidence for adequate pituitary hormone stimulation was suggestive, in that an initial 24-hour thyroidal uptake of radioactive iodine was 59 per cent.

TABLE 1. CASE #1—M. A.

Date	Serum		BMR %	Thyroidal uptake of I^{131} (%)	Treatment
	PBI* (μgm./100 ml.)	Chol. (mg./100 ml.)			
1951					
Sept. 7	2.6				
1952					
Mar. 27	4.1			59.5	
Apr. 4	5.8	247			Started sodium-*l*-thyroxine,† 0.4 mg. daily
Apr. 16	5.2	224		19.9	
June 16	4.6	294		29.0	
July 1	5.0	286	− 1		
July 6					Omitted treatment
July 8	Blood sample lost		−11		
July 15	3.0	248	− 4		
July 22	3.6	308	−31		
July 29	3.2	182	−37		
Sept. 26			−18	36.8	
Oct. 3	3.6	200			Resumed sodium-*l*-thyroxine, 0.4 mg. daily
Oct. 13	7.0	240		4.3	

* Protein-bound iodine.

† Furnished through the courtesy of Dr. Robert P. Herwick, Medical Director, Travenol Laboratories, Morton Grove, Illinois.

Treatment was planned in the form of intermittent thyroxine administration for periods of about three weeks each, at intervals of two months, in order to raise the endogenous thyroid level of activity by a method of suppression and rebound.

It seems probable, therefore, that this patient should be grouped with the cases of thyroidal hypothyroidism. But what was the defect in the thyroid? There was palpable thyroid tissue, and it could concentrate iodide, but it did not discharge thyroxine into the circulation nor did it absorb the endogenous circulating TSH indicated by the serum bio-assay.

Case #2, H.J.—Nonspecificity of symptomatology. This middle-aged man was a busy newspaper photographer who was seen at the office on February 21, 1952, because he wished a check-up to exclude stomach trouble or cancer. His gastrointestinal symptom was nausea due to not eating. No other stomach and bowel symptoms were present, except for a single loose stool with flatus after a normal daily bowel movement; there was no dysentery. Some respiratory difficulty was interpreted by the patient as asthma. He was in state of nervous tension, with his eyes swollen and weeping. Thus, his complaints were anxiety, anorexia, loose bowel movement, "asthma," and swollen lacrimating eyes. There was not much in this picture to suggest myxedema.

On physical examination the blood pressure was 100/70, and pulse 60. On carotid sinus pressure, there was cardiac arrest. He had genital ichthyotic skin. Nothing abnormal was found in the heart or in the abdomen. His prostate was of normal size. Here again, there was not much to suggest myxedema.

As part of a screening program, the laboratory work included, among other things, an electrocardiogram, and a serum protein-bound iodine determination. Laboratory findings were as follows:

Hemoglobin	15.5 grams
White blood cell count	9,000 per cu. mm.
Erythrocyte sedimentation rate	2½ mm. at one hour
Urine: Specific gravity	1.018
pH	6.0
Albumin	0
Sugar	0
Microscopic	0
Blood sugar	108 mg./100 ml.
Electrocardiogram	flat T waves
Serum protein-bound iodine	2.3 micrograms/100 ml.
Serum cholesterol	300 milligrams/100 ml.
Repeat protein-bound iodine	2.8 micrograms/100 ml.
Basal metabolic rate (unsatisfactory)	±0 per cent (pulse 60, 64)

Treatment: On April 30, 1952, the administration of sodium-*l*-thyroxine (Travenol) was started, in an oral dosage of 0.2 milligram daily. On May 27 an electrocardiogram showed normal T waves; the serum protein-bound iodine level was 5.1 micrograms per 100 ml.; and the serum cholesterol, 190 milligrams per 100 ml. Successive electrocardiograms are shown in Figure 2. On July 15, the serum protein-bound iodine level was 4.2 micrograms per 100 ml. and the serum cholesterol, 220 milligrams per 100 ml. The dosage of sodium-*l*-thyroxine was then increased to 0.4 milligram daily. On September 23, 1952, the concentration of serum protein-bound iodine was 4.4 micrograms per 100 ml. and of serum cholesterol, 215 milligrams per 100 ml. The dosage of sodium-*l*-thyroxine was increased to 0.5 milligram daily. On January 26, 1953, the level of serum protein-bound iodine was 6.4 micrograms per 100 ml. and of serum cholesterol, 202 milligrams per 100 ml.

Comment: It seems certain that this man had a severe thyroid hormone deficiency, for which he compensated by nervous drive. We suspected that the extremely active carotid sinus reflex was associated with hypothyroidism; and that he was a candidate for cerebral thrombosis or coronary-artery thrombosis (which might be prevented by thyroid therapy). Judging

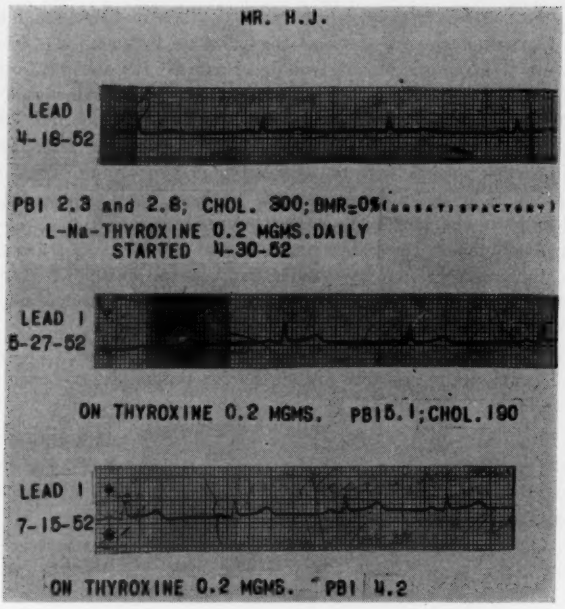

FIG. 2. The electrocardiogram in Case #2, H.J.

from results in other cases, he will require a progressive increase in thyroid medication.

DISCUSSION

These 2 cases represent severe hypothyroidism, with clinical signs and symptoms that are not usually considered to be characteristic of the disease. The clinician, then, is faced with a difficult problem in diagnosis, since he has no narrow set of symptoms that indicate to him which patient should be tested for hypothyroidism.

The first patient had a delicate and smooth skin suggestive of hyperthyroidism. She was very nervous and noticed times when she became so without obvious cause, perspired freely and had some palpitation. The second patient showed anxiety, anorexia, diarrhea, dyspnea and lacrimation.

In both patients the serum protein-bound iodine level was significantly depressed—2.6 micrograms in the first case and 2.3 micrograms in the second case. The results of other diagnostic procedures were not reliable. The basal metabolic rate in the first patient was low, but in the second patient it was normal (± 0 per cent).

It is our conclusion that determination of the serum protein-bound io-

dine level should be used as a screening procedure in all patients in whom hypothyroidism is suspected, and that the suspicion of hypothyroidism should be extended to cover a very wide category of clinical conditions. This brings the detection of hypothyroidism into line with the detection of diabetes by means of a screening glycosuric test, lues by screening serologic tests, and tuberculosis by screening x-ray procedures. It must be recognized that hypothyroidism is a systemic condition without specific symptomatology, which must be discovered by routine biochemical determinations. We urge the adoption of the serum protein-bound iodine determination as a proper method for the detection of hypothyroidism.

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Editorial

ESTROGENIC THERAPY IN GYNECOLOGY

THE estrogens are the most widely used and abused of endocrinal substances. When they are used physiologically and intelligently they are valuable preparations. However, there are those who feel that their widespread misuse may more than outweigh their value. In these random comments we shall discuss a few observations on the use of estrogens.

The ingenuity of our chemists and pharmaceutical companies has provided us with a host of preparations. In the first place there are the natural estrogens and their derivatives. The basic substances estradiol, estriol and estrone have been extracted from a variety of sources. Estradiol is the most potent naturally-occurring estrogen; estriol and estrone are much less potent, for these are the products of metabolism of estradiol. The naturally-occurring estrogens are available in pure form, in impure mixtures such as the conjugated estrogens, and as synthetic derivatives such as ethinyl estradiol. Lastly, there are the stilbene-hexane compounds, chemically unrelated to the estrogens, which have varying degrees of estrogenic activity. Diethylstilbestrol is the best known of these estrogenic drugs.

The choice of the estrogen best suited to the patient need not be a problem. The multiplicity of preparations on the market under a trade name has confused the physician to such an extent that he has lost sight of the fact that he is interested only in the estrogenic activity of the preparation. Physiologically, and thus therapeutically, there are no differences between the natural and the synthetic preparations. Although estrogens appear under a hundred different labels, the amount of estrogenic activity each preparation contains is the important factor.

Estrogens should be administered orally with but few exceptions. There are no advantages in parenteral administration and there are many disadvantages. If the physician is interested in the psychic effect of "needle" medication, there are better methods of psychosomatic therapy. Estrogens can be administered in order to accentuate their local effects. Creams are used to apply estrogens to the skin. Suppositories are useful for intravaginal medication. Implantation of estrogens in pellet form, in order to obtain a long-term effect, has not been popular in clinical practice. The physician will do well to familiarize himself with several preparations and to learn their limitations by clinical experience.

The dosage will vary with the estrogen, the mode of administration and the indication for therapy. Experience has taught us that complete substitution of ovarian function in a young woman can be attained by the

daily administration of 1 milligram of diethylstilbestrol by mouth. Obviously, if a young woman has undergone an operative procedure necessitating the loss of her ovaries, the administration of 1 milligram of diethylstilbestrol a day (or the equivalent in other estrogenic preparations), starting at the end of her first postoperative week, will suppress all menopausal symptoms indefinitely. This dose can be cut in half in six months and the patient maintained on this reduced amount indefinitely.

The patient who has some ovarian function may need much less estrogen—sufficient only to compensate for her deficiency. In some conditions, such as carcinoma of the breast, much larger doses of estrogens may be required. In pregnancy, large doses of estrogens have been administered without any unusual symptoms or complications.

The clinical use of estrogens depends entirely on their physiologic actions. Their proper application, therefore, presupposes a familiarity with their normal role in the endocrinal support of the body functions. Estrogens stimulate the growth and development of the female genital organs, the secondary sex characters and the mature skeletal pattern. In complete ovarian failure, substitution therapy by estrogens will allow the preadolescent youngster to develop into a mature woman. A maintenance dose of estrogens will assure her a normal life.

Estrogens can be regarded as specific therapy in the management of the climacteric. They will retard and cushion the transition from the active reproductive years to the postmenopausal period. They will suppress the troublesome menopausal symptoms, slow up the regression of the reproductive organs and allow a more orderly restoration of endocrinal balance.

The intelligent treatment of the patient who consults the physician because of the "change of life" should be more comprehensive than the administration of a daily pill. Such a patient should have a complete physical examination and be instructed about periodic medical examinations. Exercise and dietary instructions may be necessary in order that she may retain or regain her ideal weight. Psychosomatic therapy should include a proper mental attitude toward the changing years as well as a readjustment of the pattern of life so that the second forty years may be productive and happy.

The highly desirable therapeutic benefits of estrogens in the management of the climacteric are not without some hazard. They may induce uterine bleeding when the administration of the drug is stopped, the dose excessive, the amount varied, or even on continued administration. Some women are particularly sensitive to estrogens and, in them, these substances may induce bleeding, even when given in small amounts. Estrogenic bleeding is of no importance in itself, for it will cease with the withdrawal of the hormone. However, bleeding during the climacteric is always a suspicious

sign of cancer of the uterus and this serious condition, which can be cured in its incipiency, must not go unrecognized. Every woman who exhibits vaginal bleeding on estrogenic medication and in whom the bleeding does not stop promptly on discontinuing the hormone should have a careful pelvic examination including a curettage.

Estrogens are extremely useful in the treatment of postmenopausal vaginitis and its sequelae. The mucosal atrophy of the vagina often results in changes about the urethra and bladder, leading to bladder irritability and urinary discomfort. Small daily amounts of the hormone, such as 0.5 milligram of diethylstilbestrol orally or half this dose in a vaginal suppository, will convert the atrophic senile mucosa into a mucosa resembling that present in the mature woman, and will improve the blood supply to these areas greatly. The serosanguinous irritating vaginal discharge, the burning and smarting and the bladder discomfort disappear rapidly.

Estrogens should be administered for several weeks preoperatively to the woman in the postmenopausal period who is to have vaginal surgery. The vascularity of the tissues in this area will be improved. Mucosal ulcerations will heal rapidly and the thickened squamous epithelium will favor a normal biologic flora with a reduction in pathogenic organisms. The hormone should be continued into the postoperative period for at least six or eight weeks, in order to promote more rapid healing and a better postoperative result.

Estrogens have an anabolic effect on bone. During adolescence they hasten epiphyseal closures and bring skeletal changes to the point of maturity. They are useful in Paget's disease and in treatment of osteoporosis.

Estrogens affect the function of the anterior lobe of the pituitary gland. In laboratory animals there is an inhibition of the follicle-stimulating, the lactogenic, the growth, and possibly the thyrotropic hormones. These responses are much less evident in the human and require large doses of estrogens. The suppression of engorgement of the breasts and lactation necessitates the administration of 5 milligrams of diethylstilbestrol daily for from eight to ten days and, to be effective, it must be started immediately after delivery.

Pituitary inhibition is likewise responsible for the relief of pain in dysmenorrhea. Estrogens suppress the gonadotropic function of the pituitary and prevent ovulation. The resultant bleeding period is anovulatory in character and free from pain. The mechanism of this type of dysmenorrhea is not understood.

Estrogens have been used with varying success in the treatment of endometriosis. The rationale of this therapy is not known. The large amounts of estrogens used suppress the gonadotropic function of the pituitary gland, and inhibit cyclical activity of the ovary. The ingested estrogens cause endometrial proliferation for a time, which is followed by regression. This

may be the mechanism which induces favorable results, when they occur.

Menstrual irregularities are not treated satisfactorily with estrogens. Obviously, if either amenorrhea or excessive bleeding is the result of a mild ovarian failure, it is illogical to expect estrogens to correct this failure. It must not be forgotten that this hormone does not effect the ovary itself, but exerts its action on the target structures or through the pituitary.

Estrogens are used as a temporary expedient to stop dysfunctional uterine bleeding. In this case the therapy stimulates increased endometrial proliferation, but its withdrawal is followed by the recurrence of bleeding and much endometrial denudation. This so-called "medical curettage" may be therapeutically effective until normal ovarian function is resumed. Bleeding episodes induced in the young woman with amenorrhea are the result of the local action of estrogens on the endometrium.

Estrogens are used to neutralize the effects of androgens in the palliation of carcinoma of the breast and of the prostate. They are extremely useful in the latter condition, but results are much less decisive in breast cancer.

Estrogens have been used with varying success in a long list of clinical conditions. The good results reported for the prophylactic administration of graduated amounts of diethylstilbestrol to women during pregnancy to prevent or to ameliorate some of the hazards of early and late pregnancy, have not been substantiated in two excellent controlled studies reported recently. Estrogens will find increasing therapeutic uses but each application must be evaluated carefully before it can be recommended. More basic research into the relationships of all the steroid hormones will stimulate the more intelligent clinical use of estrogens.

The numerous beneficial effects of the therapeutic use of the estrogens are always clouded by the fear that the treatment may induce neoplasia. This is not surprising, for these hormones are the most potent growth-promoting factors that are known. However, there are no data which definitely implicate estrogens in the development of cancer. The widespread use of these hormones in small and large amounts for many years should have incriminated them more seriously as carcinogenic agents by this time. Emge, a student of this problem for a great many years, has stated that estrogens are not carcinogenic and that, at most, they may improve the soil for neoplasia in those individuals who are genetically susceptible to neoplastic growth. Intelligent treatment with estrogens is probably far less hazardous than treatment with many apparently innocuous drugs that are far less useful.

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Questions and Answers

(Questions submitted at the 1952 Postgraduate Assembly of the Endocrine Society)

Answers by C. L. Buxton, New York, N. Y.

QUESTION: Is treatment necessary in oophorectomized women who demonstrate ACTH suppression? Are other tropic hormones depressed at the same time, and is it necessary to correct the derangement?

ANSWER: We know of no evidence which indicates an association between oophorectomy and suppression of ACTH production. With regard to the depression of any other tropic hormones following oophorectomy the effect is quite the opposite in the case of gonadatropic hormones. Following either a natural menopause or surgical oophorectomy, the excretion of gonadotropic hormone is greatly increased, being usually in excess of 100 mouse units for a 24-hour specimen of urine.

QUESTION: Is it true that the cyclic use of estrogens is of importance emotionally and physiologically for reasons other than their endometrial effects?

ANSWER: It is presumed that this question is being asked concerning patients who have lost, either surgically or as a result of the menopause, their own endogenous estrogen activity.

It may be said that the cyclic use of exogenous estrogens in situations such as this will reproduce all the secondary sex characteristics provided by endogenous estrogen. This is of considerable importance physiologically and psychologically in the premenopausal woman who has undergone surgical castration. In the postmenopausal woman, however, in whom cessation of endogenous estrogen activity is physiologic and in whom the soma and the psyche amply compensate for it, exogenous estrogen therapy will produce results in terms of secondary sex characteristics which are not physiologic at this age—resumption of uterine bleeding, for instance. This may be a reason why postmenopausal estrogen therapy is inadvisable.

QUESTION: Do you use estrogen and progesterone in all cases of diabetes of pregnancy?

ANSWER: We do not use estrogen and progesterone in any cases of diabetes of pregnancy at the present time.

Answers by John E. Howard, Baltimore, Maryland

QUESTION: Please discuss the use of ACTH and cortisone in the treatment of erythema nodosum.

ANSWER: I can find little information with which to answer this question and have had experience with only 2 instances. Erythema nodosum occurs usually in association with

tuberculosis, sarcoidosis or the rheumatic group of diseases. The lesions which were present in the 2 cases seen personally cleared promptly with ACTH therapy and none recurred during the hospital stay. However, the hormone was used to treat the active underlying disease rather than the erythema nodosum.

QUESTION: Is there much chance for the psychosis to subside while treatment is continued in a patient with lupus erythematosus requiring cortisone to control it but in whom psychotic manifestations occur?

ANSWER: I don't believe this question is answerable in the present state of our knowledge. Lupus can involve the brain and one never can be sure whether it is the lupus itself or the cortisone which is causing the psychosis. In some instances in which psychosis has occurred during cortisone administration to a patient with lupus, withdrawal of cortisone has not been followed by mental clearing over a period of weeks or even months. One must be guided in the decision whether or not to continue cortisone under these circumstances by: 1) appraisal of which is worse, the psychosis or the activity of the lupus, 2) intuition, and 3) largely guess-work.

QUESTION: Please discuss the biologic and chemical determination of urinary catechol substances (epinephrine and nor-epinephrine)in pheochromocytoma.

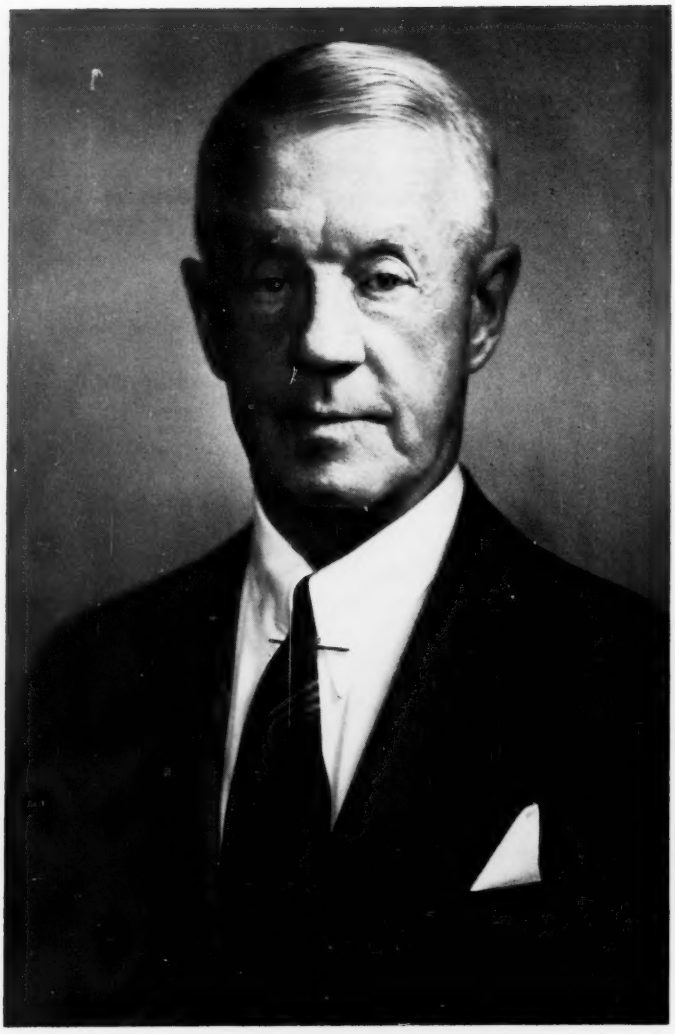
ANSWER: I haven't sufficient information to answer this question. There are reports that, by von Euler's method, pheochromocytomas have been diagnosed owing to the presence of far greater quantities of these catechol substances in the urine than are seen in the normal subject. However, these were cases readily diagnosable by other means. In small pheochromocytomas with minimal or atypical symptoms, such a test would prove most useful, but one wonders whether the normal variations have been adequately worked out. It is known that several investigators are hard at work on simpler methods which may prove diagnostically useful but, so far I know, no test with proven merit has been forthcoming.

QUESTION: Is it safe to use routinely as much as 0.05 mg. of histamine base intravenously in testing for pheochromocytoma?

ANSWER: We have not used this dose of histamine base for some years, unless the result of the test was negative when using a dose of 0.125 mg. or 0.25 mg. However, it is not known whether the larger dose will produce a greater discharge of secretions from a tumor than will the smaller dose.

QUESTION: In what percentage of normal people are small pheochromocytomas found?

ANSWER: To answer this question would require extensive study of a large series of autopsies. So far as I know, this has not been done. The condition must be relatively rare, however, for it is most unusual to find adrenal nodules of this type at postmortem examination, whereas cortical nodules are quite common.



Dr. Frank Howard Lahey

(1880–1953)

DR. FRANK HOWARD LAHEY

(June 1, 1880–June 27, 1953)

A dynamic personality has passed from the stage of American surgery. A great individual has succumbed to the ravages of time. No more will his voice be heard in the counsel of surgical progress, and no more will his aggressive mind contribute new and constructive thought to surgical advancement. His counsel and advice will be greatly missed. He stood in the field of surgery like a giant oak in the forest of surgical achievement. Great men in life are like the tremendous trees that stand out and tower above all others. One often wonders what contributes to their development. All trees draw their sustenance from the same type of soil, receive the same amount of rainfall and the same degree of sunshine, but here and there is one which stands above all those in the surrounding forest. There can be but one answer. It is not related to the soil, the rainfall, the sunshine or the environment but the unknown quality of the acorn itself. Something existed in the germ seed which, regardless of environment, destined the acorn to become an oak that, by its size, height, and gigantic proportions attracted at once the attention of all who passed its way. This well exemplifies the outstanding stature of Dr. Frank Lahey. He was a giant in the field of surgery and all who passed his way stopped to admire and revere. There was something within him that could not and would not be deterred. His inherent talents were destined to full culmination. These talents were many and were stimulated to full maturity by an indomitable zeal and by persistent application. Few have possessed so many qualities for attainment and few have developed them to such a degree of perfection. Each perfected quality stood out as a monument to his great mental capacity.

As a surgeon with an almost endless list of contributions to surgical progress, his influence has been great for many years. Few there are who have contributed so much to surgical advancement and stimulated so many in surgical thought. His mind constantly was seeking new approaches to surgical problems and new conceptions of the effect of disease.

As a teacher and lecturer he could not be excelled. He contributed enormously to the advancement of surgery through the medium of the scientific platform. His talents were always in demand and the attendance was related only to the capacity of the Assembly Hall.

His talent as an organizer and evaluator of able cooperative personnel is well attested by the renowned Clinic which he established. The steady expansion of this facility and the extent to which it has become a center for post-graduate education is a monument to his organization, executive and scientific ability.

He kept his lights trimmed and burning and never hid his talents under a bushel. They shone more brightly as the years came and went.

At the recent meeting of the American Goiter Association he conducted a never-to-be-forgotten Panel on Thyroid Disease.

It was my pleasure as President to present to him the Association's Award for Meritorious Service in the field of thyroid disease. In acknowledging this recognition he made one of the most powerful addresses of a long career, emphasizing principally the necessity for professional unity and cooperative relationship. This was recorded and will appear in the Transactions of the Association. It will be well worth reading.

It is difficult to realize that Dr. Lahey is no longer with us. I, personally, feel his passing very deeply. To me, he has been a friend of long standing, a wise counselor and a great stimulating influence. He has fulfilled the ultimate purpose of life. He has left the world better by having lived in it. He stood for high attainments, for professional unity and for scientific advancement. He was weighed in the balance and was not found wanting.

CLAUDE J. HUNT, M.D.

Kansas City, Missouri

BIOGRAPHY

(Provided by Dr. Richard Cattell, of the Lahey Clinic)

Surgeon: Born June 1, 1880, Haverhill, Massachusetts; M.D., Harvard Medical School 1904; internship, Boston City Hospital, followed by a year at the Long Island Hospital; Surgical Service, Boston City Hospital, 1905–1907; Professor of Surgery, Tufts College, 1913–1917; Professor of Clinical Surgery, Harvard Medical School, 1923–24; Director of the Lahey Clinic; Surgeon-in-Chief to the New England Baptist Hospital; Surgeon to the New England Deaconess Hospital; Trustee of Northeastern University, Tufts College, New England Baptist Hospital and New England Deaconess Hospital; Trustee, National Fund for Medical Education; Member, Council on National Emergency Medical Service.

During First World War, Major, Medical Corps, AEF, Evacuation Hospital #30; World War II, National Chairman of the Directing Board for Procurement and Assignment Service for the Armed Forces; Chairman of the Medical Consulting Board to the United States Navy; appointed Chairman for Revision of Physical Standards, 1944, by President Roosevelt; appointed to the Committee on Integration of Medical Services in the Government by President Truman in 1945.

Among the Societies: Past President, American Medical Association; Past President, New England Surgical Association; Past President, Interstate Postgraduate Medical Association; Governor, American College of Surgeons; American Surgical Society; Southern Surgical Society; American Goiter Association; Boston Surgical Society; The Endocrine Society; New England Surgical Society; Massachusetts Medical Society; The Commercial Club—The Merchants Club; The Harvard Club of Boston; The Algonquin Club, The Country Club; Brae Burn Country Club; The Bostonian Society.

Honorary Degrees and Awards

Honorary Doctor of Science degree from Tufts College in 1927.
Honorary Doctor of Science degree from Boston University in 1943.

Honorary Doctor of Science degree from Northwestern University in 1947.

Honorary Doctor of Laws Degree from University of Cincinnati in 1951.

The Medal for Merit by Secretary of the Navy, James V. Forrestal in Washington on May 17, 1946.

The Certificate of Merit by President Truman at The White House in Washington on May 17, 1946.

The Henry Jacob Bigelow Medal by the Boston Surgical Society, at Boston, Massachusetts, on May 10, 1946.

The Friedenwald Medal by the American Gastroenterological Society at Atlantic City, New Jersey, on May 25, 1946.

Honorary Fellowship, Royal College of Surgeons of England, July 31, 1947 and presented with the Degree of the College at London, September 23, 1947.

The Major Leonard Wood Medal by Boston City Hospital Alumni Association, April 29, 1950.

A citation by The American Society of Anesthesiologists for outstanding work in the advancement of anesthesia at Washington, November 7, 1951.

Nicaraguan Medal for Merit by President Somoza at Boston, June 14, 1952.

The American Goiter Association Award for Meritorious Service, at Chicago, Illinois, on May 8, 1953.

The Endocrine Society

THE 1954 ANNUAL MEETING

The Thirty-sixth Annual Meeting of The Endocrine Society will be held in the Sir Francis Drake Hotel, San Francisco, California, Thursday, Friday and Saturday, June 17–18–19, 1954.

Dr. Roberto F. Escamilla, 655 Sutter Street, San Francisco, California, is in charge of the local arrangements for the meeting.

All Scientific Sessions will be held in the Sir Francis Drake Hotel. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The annual dinner is scheduled for Friday, June 19, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

All members are urged to make hotel reservations immediately inasmuch as the hotels expect to be filled to capacity. Make reservations directly with the Sir Francis Drake Hotel, advising time of arrival and departure. Make your reservations now and avoid disappointment.

Those wishing to present papers, which will be limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. George W. Thorn, Peter Bent Brigham Hospital, Boston, Massachusetts, *not later than February 1, 1954*. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and Journals of the Society. The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each nonmember-author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of nonmembers who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.

Line 3. Institution of origin and city in which institution is located.

3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter-perfect, since there will be no opportunity for proof reading by authors.

1954 AWARDS AND FELLOWSHIPS

Awards and Fellowships presented by The Endocrine Society carry no obligation by the recipient to the Society or to the donors.

Fellowships

Society Fellowships are designed to assist men or women of exceptional promise in furthering their educational training and advancement toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $5,000 may be divided into two Fellowships in varying amounts, in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected in 1949. The Fellowship in 1950 was awarded to Dr. Lawrence E. Shulman and in 1952 to Dr. John C. Laidlaw. In 1954 it will be in the amount of $5,000.

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

This Fellowship will not be awarded in 1954 in order that it may accumulate toward a $5,000 Fellowship to be awarded in 1955.

Award

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishment of an investigator, not more than thirty-five years of age, in the field of clinical

or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; in 1949 to Dr. George Sayers; in 1950 to Dr. Oscar M. Hechter; in 1951 to Dr. Albert Segaloff. Effective in 1952, the Award was increased from $1,200 to $1,800 and the recipient was Dr. Seymour Lieberman; in 1953 the Award was presented to Drs. Sidney Roberts and Clara Szego. If within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

Nominations

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, and returned to him not later than *March 1, 1954.*

The American Goiter Association

THE 1954 ANNUAL MEETING

The Program Committee of the American Goiter Association is now in the process of formulating the program for the 1954 meeting.

Members desiring to submit papers should send six copies of a title and abstract, not to exceed 200 words, to the Chairman of the Program Committee, Dr. J. E. Rall, 444 East 68th Street, New York 21, New York, before *January 1, 1954.*

According to the Constitution, the presentation of each paper is limited to fifteen minutes, the initial discussion to four minutes and subsequent discussions to two minutes each. The Constitution also specifies that the manuscripts of all papers read at the annual meeting shall be delivered to the Secretary at the time they are presented.

The annual meeting will be held at the Somerset Hotel, Boston, Massachusetts, April 29, 30 and May 1, 1954. It is suggested that you make your hotel reservations by writing Mr. Harry Hoghn, Executive Assistant Manager, The Somerset, 400 Commonwealth Avenue, Boston 15, Massachusetts.

JOHN C. MCCLINTOCK, M.D.,
Corresponding and Recording Secretary

VAN METER PRIZE AWARD FOR 1954

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held in Boston, Massachusetts, April 29, 30 and May 1, 1954, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English, and a typewritten double-spaced copy in duplicate sent to the Corresponding Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York, not later than *January 15, 1954.* The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the Prize Award Essay by the author, if it is possible for

him to attend. The essay will be published in the annual Transactions of the Association.

AWARD OF MERIT FOR 1954

TO ALL MEMBERS OF THE AMERICAN GOITER ASSOCIATION

An anonymous gift of $1,000 to be awarded each year for three years has been accepted by the Executive Council of The American Goiter Association. The terms of the gift specify that this sum shall be given to a member of the Association under 45 years of age who has made the most important contributions to the knowledge and understanding of thyroid disease or the treatment of thyroid disease.

Candidates for this award are to be nominated by members of the Association. When making a nomination, complete details of the nominee's present and past positions and training must be submitted. A complete bibliography of the nominee's publications is required. A full explanation of the reasons for nominating the candidate must be given.

The candidates submitted are to be reviewed by an anonymous committee appointed by the president. The chairman of this committee will present the deliberations and decisions of said committee to the Executive Council in advance of the annual meeting.

The award is to be called The American Goiter Association Award of Merit and shall be presented at the annual banquet.

You are requested to send two copies of your nominations to this secretary, making certain the information required by the deed of gift is included. All nominations must be received not later than *February 1, 1954.*

JOHN C. MCCLINTOCK, M.D.,
Recording and Corresponding Secretary

149½ Washington Avenue,
Albany 10, N. Y.

RECIPIENTS OF VAN METER PRIZE AWARD FOR 1953

Van Meter Prize

The Van Meter Prize for 1953 was awarded to *Dr. Belton A. Burrows* for the essay, with Dr. Joseph F. Ross, entitled "The Thyroidal Uptake of Stable Iodine Compared with the Serum Concentration of Protein-bound Iodine in Normal Subjects and in Patients with Thyroid Disease."

Dr. Burrows was born March 3, 1918, at Poquonnock Bridge, Connecticut. He received the A.B. degree from Yale in 1939 and the M.D. degree from Columbia University College of Physicians and Surgeons in 1943. He was Intern and then Assistant Resident in Internal Medicine at the New Haven Hospital, New Haven, Conn., 1943–1944 and 1946–1947, respec-

tively. During the period 1944–1946 he was 1st Lieutenant and Captain, M.C., A.U.S. From 1947 to 1950 he was Assistant Resident in Medicine and Life Insurance Medical Research Fellow at the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, Boston, Massachusetts. Since 1950 he has been Senior Physician, Radioisotope Unit, Boston Veterans Administration Hospital; Associate Member, Robert Dawson Evans Memorial; and Assistant Professor, Boston University School of Medicine, Boston, Massachusetts.

Dr. Ross was born October 11, 1910, in Azusa, California. He received the A.B. degree from Stanford in 1933 and the M.D. degree from Harvard Medical School in 1936. From 1936 to 1940 he was Intern in Medicine, Boston City Hospital; and then Resident in Pathology, Mallory Institute (Boston City Hospital), Boston, Massachusetts, and Strong Memorial Hospital, Rochester, New York. At present he is Physician, Massachusetts Memorial Hospitals; Member, Robert Dawson Evans Memorial; Associate Professor of Medicine, Boston University School of Medicine; and Director, Radioisotope Unit, Boston Veterans Administration Hospital, Boston, Massachusetts.

First Honorable Mention

First Honorable Mention was given to the essay by *Dr. Sidney H. Ingbar*, entitled "The Simultaneous Measurement of the Iodide-Concentrating and Protein-Binding Capacities of the Human Thyroid Gland."

Dr. Ingbar was born February 12, 1925, in Denver, Colorado. He attended the University of California at Los Angeles during the period 1941–1943 and received the M.D. degree from Harvard Medical School in 1947. He was Intern and then Assistant Resident in Medicine on the 2nd and 4th Medical Services, Boston City Hospital, from 1947 to 1949. From 1949 to 1951 he was a Research Fellow in Medicine (Endocrinology) at the Harvard Medical School and the Thorndike Memorial Laboratory, Boston City Hospital. He was a Captain in the Army Medical Corps, assigned to Army Medical Service Graduate School, Washington, D. C., from 1951 to 1953. At present he is Instructor in Medicine, Harvard Medical School; American College of Physicians Fellow in Medicine; and Assistant Physician, Thorndike Memorial Laboratory, Boston City Hospital, Boston, Massachusetts.

Second Honorable Mention

Second Honorable Mention was given to the essay by *Dr. Jacob Robbins*, entitled "Identification of Thyroglobulin in Human Serum after Large Doses of I^{131}." Dr. Robbins was born in Yonkers, New York, in 1922. He received the A.B. degree from Cornell University in 1944 and the M.D. degree from Cornell University Medical College in 1947. After internship at New York Hospital in 1947–1948, he was Resident at Memorial Hospital, New York, from 1948 to 1950. He was a Damon Runyon Fellow at Me-

morial Center from 1949 to 1952, and now is Research Fellow at the Sloan-Kettering Institute, Clinical Assistant in Medicine at Memorial Center, and Instructor in Medicine at Cornell University Medical College.

RECIPIENTS OF AWARDS FOR MERITORIOUS SERVICE

In 1951 at its annual business meeting the American Goiter Association established by unanimous vote an award to be given each year to one or more of its members who had devoted many years of interest and work on behalf of the American Goiter Association. The first member of the Association to receive a certificate signifying this interest in the Association was *André Crotti, M.D.*, born in Switzerland, graduated from the Université de Lausanne Faculté de Médecine, author of many books and articles dealing with the subject of goiter, and head of the clinic that bears his name in Columbus, Ohio, where he has been engaged in the practice of surgery for more than thirty years.

In 1952 the certificate was given to *James A. Hill, M.D.*, who has long practiced surgery in Houston, Texas, was graduated from Tulane University of Louisiana School of Medicine in 1900 and whose interest in the American Goiter Association has been duly long and meritorious.

In 1953 *Frank H. Lahey, M.D.* and *Nelson M. Percy, M.D.* were each awarded the certificate signifying their long service to the American Goiter Association.

At the age of 47 *George C. Shivers, M.D.* of Colorado Springs, Colorado, died suddenly of heart disease after serving the Association for sixteen years as its secretary. By action of the Executive Council a certificate of long and meritorious service was forwarded to his widow as a small token of the appreciation felt by the Association for the many years Dr. Shivers had devoted to its work.

American Society for the Study of Sterility Award for Outstanding Research in the Field of Infertility

The American Society for the Study of Sterility announces the opening of the 1954 contest for the most outstanding contribution to the subject of infertility and sterility. The winner will receive a cash award of one thousand dollars, and the essay will appear on the program of the 1954 meeting of the Society. Essays submitted in this competition must be received not later than *March 1, 1954*. For full particulars concerning requirements of this competition, address The American Society for the Study of Sterility, c/o Dr. Herbert H. Thomas, Secretary, 920 South 19th Street, Birmingham, Alabama.

The author should append on a separate sheet of paper a short biographical sketch of himself and include a photograph to be used in the necessary publicity should he be the winner of the award.